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PATENT APPLICATION

Date of Deposit: June 20, 2000

Attorney Docket No. 00960-503 CIP FWC2 DIV

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANTS : Thangavel KUBERSAMPATH, Roy H.L. PANG, Herrmann
OPPERMANN, David C. RUEGER, Charles M. COHEN, John E.
SMART
EXAMINER : Not yet assigned
FILING DATE : Herewith
FOR: METHOD FOR REDUCING TISSUE DAMAGE ASSOCIATED WITH
ISCHEMIA-REPERFUSION OR HYPOXIA INJURY

jc531 U.S. PTO

09/597517

06/20/00

Box PATENT APPLICATION
Assistant Commissioner of Patents
Washington, D.C. 20231

REQUEST FOR CONTINUATION PATENT APPLICATION
PURSUANT TO 37 C.F.R. 1.53(b)

1. This is a request for a filing of a divisional application under 37 C.F.R. 1.53(b) of non-provisional patent application U.S.S.N. 08/445,467, filed on May 22, 1995, entitled:

**METHOD FOR REDUCING TISSUE DAMAGE ASSOCIATED WITH ISCHEMIA-
REPERFUSION OR HYPOXIA INJURY**

Application 08/445,467 is a continuation of U.S.S.N. 08/165,511, filed 12/9/93 (Abandoned), which is a continuation of U.S.S.N. 07/938,336, filed 8/28/92 (Abandoned), which is a CIP of U.S.S.N. 07/753,059, filed 8/30/91 (Abandoned), which is a CIP of U.S.S.N. 07/667,274, filed 3/11/91 (Abandoned), said U.S.S.N. 07/938,336 (filed 8/28/92) also a CIP of U.S.S.N. 07/752,764, filed 8/30/91 (Abandoned), which is a CIP of U.S.S.N. 07/667,274, filed 3/11/91 (Abandoned).

2. ☒ Patent Application - Total pages (147 pages), wherein:
Specification (138 pages); Claims (8 pages); Abstract (1 page)
3. ☒ Sequence Listing
☒ Statement Requesting Use of Previously Filed Sequence Information
pursuant to 37 C.F.R. 1.821(e).
4. ☒ Drawings
☒ Informal - six (6) sheets (FIGS. 1-6)

5. ☒ Information Disclosure Statements (IDS) and Notices of References Cited
- ☒ Copy of Information Disclosure Statement and PTO-1449 from prior application, submitted January 22, 1993 (6 pages).
 - ☒ Copy of Supplemental Information Disclosure Statement and PTO-1449 from prior application, submitted February 11, 1993 (3 pages).
 - ☒ Copy of Information Disclosure Statement and PTO-1449 from prior application, submitted January 22, 1993 (5 pages). May 22, 1995
 - ☒ Copy of Supplemental Information Disclosure Statement and PTO-1449 from prior application, submitted August 29, 1997 (5 pages).
 - ☒ Copies of Notice of References Cited (3 pages)

6. Fee Calculation

- A. ☒ Regular application

CLAIMS AS FILED					
Claims	Number Filed	Basic Fee Allowance	Number Extra	Rate	Basic Fee 37 C.F.R. 1.16(a) \$690.00
Total Claims (37 C.F.R. 1.16(c))	5	- 20 =	0	\$ 18.00	.00
Independent Claims (37 C.F.R. 1.16(b))	3	- 3 =		\$ 78.00	.00
Multiple Dependent Claim(s), if any (37 C.F.R. 1.16(d))	0			\$260.00	
SUBTOTAL:					.00
Reduction by 50% for filing by small entity:					- \$.00
TOTAL FEE					\$690.00

7. Declaration and Power of Attorney:
- ☒ Copy of Combined Declaration and Power of attorney from parent application U.S.S.N. 07/938,336 (8 pages)
 - ☒ Copy of Revocation by Assignee and new Power of Attorney Dated October 11, 1999 from prior application (2 pages)
8. ☒ Original Assignment from U.S.S.N. 07/938,336 assigning all rights to Creative Biomolecules, Inc. (4 pages).

9. ☒ Preliminary Amendment (48 pages)

10. ☒ Postcard

Respectfully submitted,



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Dated: June 20, 2000

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PATENT APPLICATION
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FOR: METHOD FOR REDUCING TISSUE DAMAGE ASSOCIATED WITH
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Assistant Commissioner of Patents
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PRELIMINARY AMENDMENT

Prior to examination of the above-identified application, please amend the application as follows.

In the Title:

Please replace “MORPHOGEN-INDUCED MODULATION OF INFLAMMATORY RESPONSE” with --METHOD FOR REDUCING TISSUE DAMAGE ASSOCIATED WITH ISCHEMIA-REPERFUSION OR HYPOXIA INJURY--

In the Specification:

On page 1, line 2 replace: “CRP-059” with --CBM-3 CIPFWC2DIV-- and delete line 3 “(2054/28)”

On page 1, replace lines 11- 16 with: --This application is a divisional of U.S.S.N. 08/445,467, filed on May 22, 1995, which is a continuation of U.S.S.N. 08/165,511, filed 12/9/93 (Abandoned), which is a continuation of U.S.S.N. 07/938,336, filed 8/28/92 (Abandoned), which is a CIP of U.S.S.N. 07/753,059, filed 8/30/91 (Abandoned), which is a CIP of U.S.S.N. 07/667,274, filed 3/11/91 (Abandoned), said U.S.S.N. 07/938,336 (filed 8/28/92) also a CIP of U.S.S.N. 07/752,764, filed 8/30/91 (Abandoned), which is a CIP of U.S.S.N.

07/667,274, filed 3/11/97 (Abandoned).--

Replace pages 98-138 with substitute pages 95-138.

In the Claims:

Cancel claims 1-2, 4-22, and 24-48.

Amend claims 3 and 23 as follows:

3. (Amended) [The method of claim 1 where said step of providing a therapeutically effective morphogen concentration to said injured tissue comprises the step of] A method for alleviating tissue destructive effects associated with an inflammatory response to an injured tissue in a mammal, comprising administering to said mammal an agent that stimulates *in vivo* a therapeutically effective concentration of an endogenous morphogen.

~~23.~~ (Amended) [The method of claim 20 or 21] A method for reducing tissue damage associated with ischemia-reperfusion injury in a human, the method comprising the step of providing to an injured tissue a therapeutic concentration of a morphogen sufficient to alleviate the damage associated with said injury, wherein said step of providing a therapeutically effective morphogen concentration to said injured tissue comprises [the step of] administering to said mammal an agent that stimulates *in vivo* a therapeutically effective concentration of an endogenous morphogen.

Add new claim 49.

~~--49.~~ (new) A method for reducing tissue damage associated with hyperoxia injury in a human, the method comprising the step of providing to an injured tissue a therapeutic concentration of a morphogen sufficient to alleviate the damage associated with said injury, wherein said step of providing a therapeutically effective morphogen concentration to said injured tissue comprises administering to said mammal an agent that stimulates *in vivo* a therapeutically effective concentration of an endogenous morphogen.

REMARKS

This preliminary amendment is being filed concurrently with a divisional application of co-pending application 08/445,467, filed on May 22, 1995.

Claims 3, 23, and 49 are pending. Claims 1-2, 4-22, and 24-48 have been canceled as being drawn to a non-elected invention. Claim 3 was amended to incorporate the limitations of claim 1 (from which it originally depended), thus putting the claim into independent form. Claim 23 was amended to incorporate the limitations of claim 20 (from which it originally depended), thus putting the claim into independent form. New claim 49 was added. This claim incorporates the limitations of originally filed claim 23 and claim 21, from which claim 23 originally depended.

Minor amendments of a clerical nature were made to the Specification. In particular, the title has been amended to more accurately reflect the subject matter of the invention and to correspond to the amended title in sister application 08/445,467, filed on May 22, 1995. Additionally, Cross-Reference to Related Applications has been corrected. On page 1, an amendment has been made to the attorney reference, and extraneous attorney docket numbers have been deleted.

An amendment to the sequence information has been made by substituting pages 95-138. This amendment corresponds to an amendment made on April 16, 1993 in parent application 07/938,336. No new matter has been added.

CONCLUSION

On the basis of the foregoing amendments, Applicants respectfully submit that the application is in condition for allowance. Allowance of this application by the Examiner is hereby requested.

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If there are any questions regarding these amendments and remarks, the Examiner is encouraged to contact either of the undersigned at the telephone number provided below.

W. B. Bessie

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TRADOCS:1343084.1(SSBW01!.DOC)

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**MORPHOGEN-INDUCED MODULATION OF
INFLAMMATORY RESPONSE**

Cross Reference Relationship to Related Applications

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This application is a continuation-in-part of
(1) USSN 753,059, filed August 30, 1991, which is a
continuation-in-part of USSN 667,274, filed March 11,
1991, (2) USSN 752,764, filed August 30, 1991, which is
a continuation-in-part of USSN 667,274 and [Atty.
Docket No. CRP-068] filed on even date herewith.

Field of the Invention

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The present invention relates generally to a method
for modulating the inflammatory response induced in a
mammal following tissue injury. More particularly,
this invention relates to a method for alleviating
immune-cell mediated tissue destruction associated with
the inflammatory response.

Background of the Invention

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The body's inflammatory response to tissue injury
can cause significant tissue destruction, leading to
loss of tissue function. Damage to cells resulting
from the effects of inflammatory response e.g., by
immune-cell mediated tissue destruction, has been
implicated as the cause of reduced tissue function or
loss of tissue function in diseases of the joints

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(e.g., rheumatoid and osteo-arthritis) and of many organs, including the kidney, pancreas, skin, lung and heart. For example, glomular nephritis, diabetes, inflammatory bowel disease, vascular diseases such as atherosclerosis and vasculitis, and skin diseases such as psoriasis and dermatitis are believed to result in large part from unwanted acute inflammatory reaction and fibrosis. A number of these diseases, including arthritis, psoriasis and inflammatory bowel disease are considered to be chronic inflammatory diseases. The damaged tissue also often is replaced by fibrotic tissue, e.g., scar tissue, which further reduces tissue function. Graft and transplanted organ rejection also is believed to be primarily due to the action of the body's immune/inflammatory response system.

The immune-cell mediated tissue destruction often follows an initial tissue injury or insult. The secondary damage, resulting from the inflammatory response, often is the source of significant tissue damage. Among the factors thought to mediate these damaging effects are those associated with modulating the body's inflammatory response following tissue injury, e.g., cytokines such as interleukin-1 (IL-1) and tumor necrosis factor (TNF), and oxygen-derived free radicals such as superoxide anions. These humoral agents are produced by adhering neutrophilic leukocytes or by endothelial cells and have been identified at ischemic sites upon reperfusion. Moreover, TNF concentrations are increased in humans after myocardial infarction.

A variety of lung diseases are characterized by airway inflammation, including chronic bronchitis, emphysema, idiopathic pulmonary fibrosis and asthma.

Another type of lung-related inflammation disorders are inflammatory diseases characterized by a generalized, wide-spread, acute inflammatory response such as adult respiratory distress syndrome. Another dysfunction

5 associated with the inflammatory response is that mounted in response to injury caused by hyperoxia, e.g., prolonged exposure to lethally high concentrations of O_2 (95-100% O_2). Similarly, reduced blood flow to a tissue (and, therefore reduced or lack
10 of oxygen to tissues), as described below, also can induce a primary tissue injury that stimulates the inflammatory response.

15 It is well known that damage occurs to cells in mammals which have been deprived of oxygen. In fact, the interruption of blood flow, whether partial (hypoxia) or complete (ischemia) and the ensuing inflammatory responses may be the most important cause of coagulative necrosis or cell death in human disease.
20 The complications of atherosclerosis, for example, are generally the result of ischemic cell injury in the brain, heart, small intestines, kidneys, and lower extremities. Highly differentiated cells, such as the proximal tubular cells of the kidney, cardiac myocytes,
25 and the neurons of the central nervous system, all depend on aerobic respiration to produce ATP, the energy necessary to carry out their specialized functions. When ischemia limits the oxygen supply and ATP is depleted, the affected cells may become
30 irreversibly injured. The ensuing inflammatory responses to this initial injury provide additional insult to the affected tissue. Examples of such hypoxia or ischemia are the partial or total loss of blood supply to the body as a whole, an organ within
35 the body, or a region within an organ, such as occurs

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The tissue damage associated with ischemia-reperfusion injury is believed to comprise both the initial cell damage induced by the deprivation of oxygen to the cell and its subsequent recirculation, as well as the damage caused by the body's response to this initial damage. It is thought that reperfusion injury may result in dysfunction to the endothelium of the vasculature as well as injury to the surrounding tissue. In idiopathic pulmonary fibrosis, for example, scar tissue accumulates on the lung tissue lining, inhibiting the tissue's elasticity. The tissue damage associated with hyperoxia injury is believed to follow a similar mechanism, where the initial damage is mediated primarily through the presence of toxic oxygen metabolites, followed by an inflammatory response to this initial injury.

Similarly, tissues and organs for transplantation also are subject to the tissue destructive effects associated with the recipient host body's inflammatory response following transplantation. It is currently believed that the initial destructive response is due in large part to reperfusion injury to the transplanted organ after it has been transplanted to the organ recipient.

Accordingly, the success of organ or tissue transplantation depends greatly on the preservation of the tissue activity (e.g., tissue or organ viability) at the harvest of the organ, during storage of the harvested organ, and at transplantation. To date, preservation of organs such as lungs, pancreas, heart

and liver remains a significant stumbling block to the successful transplantation of these organs. U.S. Patent No. 4,952,409 describes a superoxide dismutase-containing liposome to inhibit reperfusion injury.

5 U.S. Patent No. 5,002,965 describes the use of ginkgolides, known platelet activating factor antagonists, to inhibit reperfusion injury. Both of these factors are described as working primarily by inhibiting the release of and/or inhibiting the
10 damaging effects of free oxygen radicals. A number of patents also have issued on the use of immunosuppressants for inhibiting graft rejection. A representative listing includes U.S. Patent Nos. 5,104,858, 5,008,246 and 5,068,323. A significant
15 problem with many immunosuppressants is their low therapeutic index, requiring the administration of high doses that can have significant toxic side effects.

Rheumatoid and osteoarthritis are prevalent
20 diseases characterized by chronic inflammation of the synovial membrane lining the afflicted joint. A major consequence of chronic inflammatory joint disease (e.g., rheumatoid arthritis) and degenerative arthritis (e.g., osteoarthritis) is loss of function of those
25 affected joints. This loss of function is due primarily to destruction of the major structural components of the joint, cartilage and bone, and subsequent loss of the proper joint anatomy. As a consequence of chronic disease, joint destruction
30 ensues and can lead to irreversible and permanent damage to the joint and loss of function. Current treatment methods for severe cases of rheumatoid arthritis typically include the removal of the synovial membrane, e.g., synovectomy. Surgical synovectomy has
35 many limitations, including the risk of the surgical

procedure itself, and the fact that a surgeon often cannot remove all of the diseased membrane. The diseased tissue remaining typically regenerates, causing the same symptoms which the surgery was meant to alleviate.

Psoriasis is a chronic, recurrent, scaling skin disease of unknown etiology characterized by chronic inflammation of the skin. Erythematous eruptions, often in papules or plaques, and usually having a white silvery scale, can affect any part of the skin, but most commonly affect the scalp, elbows, knees and lower back. The disease usually occurs in adults, but children may also be affected. Patients with psoriasis have a much greater incidence of arthritis (psoraitic arthritis), and generalized exfoliation and even death can threaten afflicted individuals.

Current therapeutic regimens include topical or intralesional application of corticosteroids, topical administration of keratolytics, and use of tar and UV light on affected areas. No single therapy is ideal, and it is rare for a patient not to be treated with several alternatives during the relapsing and remitting course of the disease. Whereas systematic treatment can induce prompt resolution of psoriatic lesions, suppression often requires ever-increasing doses, sometimes with toxic side effect, and tapering of therapy may result in rebound phenomena with extensions of lesions, possibly to exfoliation.

Inflammatory bowel disease (IBD) describes a class of clinical disorders of the gastrointestinal mucosa characterized by chronic inflammation and severe ulceration of the mucosa. The two major diseases in

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this classification are ulcerative colitis and regional enteritis (Crohn's Disease). Like oral mucositis, the diseases classified as IBD are associated with severe mucosal ulceration (frequently penetrating the wall of the bowel and forming strictures and fistulas), severe mucosal and submucosal inflammation and edema, and fibrosis (e.g., scar tissue formation which interferes with the acid protective function of the gastrointestinal lining.) Other forms of IBD include regional ileitis and proctitis. Clinically, patients with fulminant IBD can be severely ill with massive diarrhea, blood loss, dehydration, weight loss and fever. The prognosis of the disease is not good and frequently requires resection of the diseased tissue.

Therefore, an object of the present invention is to provide a method for protecting mammalian tissue, particularly human tissue, from the damage associated with the inflammatory response following a tissue injury. The inflammatory reaction may be in response to an initial tissue injury or insult. The original injury may be chemically, mechanically, immunologically or biologically related. Another object is to provide methods and compositions for protecting tissue from the tissue destructive effects associated with chronic inflammatory diseases, including arthritis (e.g., rheumatoid or osteoarthritis), psoriatic arthritis, psoriasis and dermatitis, inflammatory bowel disease and other autoimmune diseases.

Another object of the invention is to provide methods and compositions for enhancing the viability of mammalian tissues and organs to be transplanted, including protecting the transplanted organs from immune cell-mediated tissue destruction, such as the

tissue damage associated with ischemia-reperfusion injury, such as can occur upon initiation of blood flow after transplantation of the organ in the recipient host.

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Another object of the invention is to provide a method for alleviating tissue damage associated with ischemic-reperfusion injury in a mammal following a deprivation of oxygen to a tissue in the mammal. Other
10 objects of the present invention include providing a method for alleviating tissue damage associated with ischemic-reperfusion injury in a human which has suffered from hypoxia or ischemia following cardiac arrest, pulmonary embolus, renal artery occlusion,
15 coronary occlusion or occlusive stroke, as well as tissue damage associated with a surgical or other aggressive clinical procedure. Still another object is to provide a method for alleviating tissue damage associated with hyperoxia-induced injury in a human
20 following exposure to lethally high oxygen concentrations.

Still another object of the invention is to provide a method for modulating inflammatory responses in
25 general, particularly those induced in a human following tissue injury.

These and other objects and features of the invention will be apparent from the description,
30 drawings and claims which follow.

Summary of the Invention

5 The present invention provides a method for
alleviating the tissue destructive effects associated
with activation of the inflammatory response following
tissue injury. The method comprises the step of
providing to the affected tissue a therapeutically
effective concentration of a morphogenic protein
("morphogen", as defined herein) upon tissue injury or
10 in anticipation of tissue injury, sufficient to
substantially inhibit or reduce the tissue destructive
effects of the inflammatory response.

15 In one aspect, the invention features compositions
and therapeutic treatment methods that comprise the
step of administering to a mammal a therapeutically
effective amount of a morphogenic protein
("morphogen"), as defined herein, upon injury to a
tissue, or in anticipation of such injury, for a time
20 and at a concentration sufficient to inhibit the tissue
destructive effects associated with the body's
inflammatory response, including repairing damaged
tissue, and/or inhibiting additional damage thereto.

25 In another aspect, the invention features
compositions and therapeutic treatment methods for
protecting tissues and organs from the tissue
destructive effects of the inflammatory response which
include administering to the mammal, upon injury to a
30 tissue or in anticipation of such injury, a compound
that stimulates in vivo a therapeutically effective
concentration of an endogenous morphogen within the
body of the mammal sufficient to protect the tissue
from the tissue destructive effects associated with the
35 inflammatory response, including repairing damaged

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tissue death, particularly immune cell-mediated tissue death. "Transplanted" living tissue includes both tissue transplants, (e.g., as in the case of bone marrow transplants, for example), and tissue grafts.

5 Finally, a "free oxygen radical inhibiting agent" means a molecule capable of inhibiting the release of and/or inhibiting the tissue damaging effects of free oxygen radicals.

10 In one embodiment of the invention, the invention provides methods and compositions for alleviating the ischemic-reperfusion injury in mammalian tissue resulting from a deprivation of, and subsequent reperfusion of, oxygen to the tissue. In another
15 embodiment, the invention provides a method for alleviating the tissue-destructive effects associated with hyperoxia. In still another embodiment of the invention, the invention provides methods and
20 compositions for maintaining the viability of tissues and organs, particularly transplanted tissues and organs, including protecting these tissues and organs from ischemia-reperfusion injury. In still another embodiment, the invention provides methods for
25 protecting tissues and organs from the tissue destructive effects of chronic inflammatory diseases, such as arthritis, psoriasis, dermatitis, including contact dermatitis, IBD and other chronic inflammatory diseases of the gastrointestinal tract, as well as the
30 tissue destructive effects associated with other, known autoimmune diseases, such as diabetes, multiple sclerosis, amyotrophic lateral sclerosis (ALS), and other autoimmune neurodegenerative diseases.

In one aspect of the invention, the morphogen is
35 provided to the damaged tissue following an initial

injury to the tissue. The morphogen may be provided directly to the tissue, as by injection to the damaged tissue site or by topical administration, or may be provided indirectly, e.g., systemically by oral or parenteral means. Alternatively, as described above, an agent capable of stimulating endogenous morphogen expression and/or secretion may be administered to the mammal. Preferably, the agent can stimulate an endogenous morphogen in cells associated with the damaged tissue. Alternatively, morphogen expression and/or secretion may be stimulated in a distant tissue and the morphogen transported to the damaged tissue by the circulatory system.

In another aspect of the invention, the morphogen is provided to tissue at risk of damage due to immune cell-mediated tissue destruction. Examples of such tissues include tissue grafts and transplanted tissue or organs, as well as any tissue or organ about to undergo a surgical procedure or other clinical procedure likely to either inhibit blood flow to the tissue or otherwise induce an inflammatory response. Here the morphogen or morphogen-stimulating agent preferably is provided to the patient prior to induction of the injury, e.g., as a prophylactic, to provide a cyto-protective effect to the tissue at risk.

The morphogens described herein are envisioned to be useful in enhancing viability of any organ or living tissue to be transplanted. The morphogens may be used to particular advantage in lung, heart, kidney, liver and pancreas transplants, as well as in transplantation and/or grafting of skin, gastrointestinal mucosa, bone marrow and other living tissues.

Where the patient suffers from a chronic inflammatory disease, such as diabetes, arthritis, psoriasis, IBD, and the like, the morphogen or morphogen-stimulating agent preferably is administered at regular intervals as a prophylactic, to prevent and/or inhibit the tissue damage normally associated with the disease during flare periods. As above, the morphogen or morphogen-stimulating agent may be provided directly to the tissue at risk, for example by injection or by topical administration, or indirectly, as by systemic e.g., oral or parenteral administration.

Among the morphogens useful in this invention are proteins originally identified as osteogenic proteins, such as the OP-1, OP-2 and CBMP2 proteins, as well as amino acid sequence-related proteins such as DPP (from *Drosophila*), Vgl (from *Xenopus*), Vgr-1 (from mouse, see U.S. 5,011,691 to Oppermann et al.), GDF-1 (from mouse, see Lee (1991) PNAS 88:4250-4254), all of which are presented in Table II and Seq. ID Nos.5-14), and the recently identified 60A protein (from *Drosophila*, Seq. ID No. 24, see Wharton et al. (1991) PNAS 88:9214-9218.) The members of this family, which include members of the TGF- β super-family of proteins, share substantial amino acid sequence homology in their C-terminal regions. The proteins are translated as a precursor, having an N-terminal signal peptide sequence, typically less than about 30 residues, followed by a "pro" domain that is cleaved to yield the mature sequence. The signal peptide is cleaved rapidly upon translation, at a cleavage site that can be predicted in a given sequence using the method of Von Heijne ((1986) Nucleic Acids Research 14:4683-4691.) Table I, below, describes the various morphogens identified to date, including their nomenclature as

used herein, their Seq. ID references, and publication sources for the amino acid sequences for the full length proteins not included in the Seq. Listing. The disclosure of these publications is incorporated herein
5 by reference.

TABLE I

10	"OP-1"	Refers generically to the group of morphogenically active proteins expressed from part or all of a DNA sequence encoding OP-1 protein, including allelic and species variants thereof, e.g., human OP-1 ("hOP-1", Seq. ID No. 5, mature protein amino acid sequence), or mouse OP-1 ("mOP-1", Seq. ID No. 6, mature protein amino acid sequence.) The conserved seven cysteine skeleton is defined by residues 38 to 139 of Seq. ID Nos. 5 and 6. The cDNA sequences and the amino acids encoding the full length proteins are provided in Seq. Id Nos. 16 and 17 (hOP1) and Seq. ID Nos. 18 and 19 (mOP1.) The mature proteins are defined by residues 293-431 (hOP1) and 292-430 (mOP1). The "pro" regions of the proteins, cleaved to yield the mature, morphogenically active proteins are defined essentially by residues 30-292 (hOP1) and residues 30-291 (mOP1).
30	"OP-2"	refers generically to the group of active proteins expressed from part or all of a DNA sequence encoding OP-2 protein, including allelic and species variants thereof, e.g., human OP-2 ("hOP-2", Seq.
35		

ID No. 7, mature protein amino acid sequence) or mouse OP-2 ("mOP-2", Seq. ID No. 8, mature protein amino acid sequence). The conserved seven cysteine skeleton is defined by residues 38 to 139 of Seq. ID Nos. 7 and 8. The cDNA sequences and the amino acids encoding the full length proteins are provided in Seq. ID Nos. 20 and 21 (hOP2) and Seq. ID Nos. 22 and 23 (mOP2.) The mature proteins are defined essentially by residues 264-402 (hOP2) and 261-399 (mOP2). The "pro" regions of the proteins, cleaved to yield the mature, morphogenically active proteins likely are defined essentially by residues 18-263 (hOP2) and residues 18-260 (mOP2). (Another cleavage site also occurs 21 residues upstream for both OP-2 proteins.)

"CBMP2"

refers generically to the morphogenically active proteins expressed from a DNA sequence encoding the CBMP2 proteins, including allelic and species variants thereof, e.g., human CBMP2A ("CBMP2A(fx)", Seq ID No. 9) or human CBMP2B DNA ("CBMP2B(fx)", Seq. ID No. 10). The amino acid sequence for the full length proteins, referred to in the literature as BMP2A and BMP2B, or BMP2 and BMP4, appear in Wozney, et al. (1988) Science 242:1528-1534. The pro domain for BMP2 (BMP2A) likely includes residues 25-248 or 25-282; the mature protein, residues 249-396 or 283-396. The pro domain for BMP4 (BMP2B)

likely includes residues 25-256 or 25-292;
the mature protein, residues 257-408 or
293-408.

5 "DPP(fx)" refers to protein sequences encoded by the
Drosophila DPP gene and defining the
conserved seven cysteine skeleton (Seq. ID
No. 11). The amino acid sequence for the
full length protein appears in Padgett, et
10 al (1987) Nature 325: 81-84. The pro
domain likely extends from the signal
peptide cleavage site to residue 456; the
mature protein likely is defined by
residues 457-588.

15 "Vgl(fx)" refers to protein sequences encoded by the
Xenopus Vgl gene and defining the
conserved seven cysteine skeleton (Seq. ID
No. 12). The amino acid sequence for the
full length protein appears in
20 Weeks (1987) Cell 51: 861-867. The
prodomain likely extends from the signal
peptide cleavage site to residue 246; the
mature protein likely is defined by
residues 247-360.

25 "Vgr-1(fx)" refers to protein sequences encoded by the
murine Vgr-1 gene and defining the
conserved seven cysteine skeleton (Seq. ID
No. 13). The amino acid sequence for the
full length protein appears in Lyons, et
30 al, (1989) PNAS 86: 4554-4558. The
prodomain likely extends from the signal
peptide cleavage site to residue 299; the
mature protein likely is defined by
35 residues 300-438.

"GDF-1(fx)" refers to protein sequences encoded by the human GDF-1 gene and defining the conserved seven cysteine skeleton (Seq. ID No. 14). The cDNA and encoded amino sequence for the full length protein is provided in Seq. ID. No. 32. The prodomain likely extends from the signal peptide cleavage site to residue 214; the mature protein likely is defined by residues 215-372.

"60A" refers generically to the morphogenically active proteins expressed from part or all of a DNA sequence (from the Drosophila 60A gene) encoding the 60A proteins (see Seq. ID No. 24 wherein the cDNA and encoded amino acid sequence for the full length protein is provided). "60A(fx)" refers to the protein sequences defining the conserved seven cysteine skeleton (residues 354 to 455 of Seq. ID No. 24.) The prodomain likely extends from the signal peptide cleavage site to residue 324; the mature protein likely is defined by residues 325-455.

"BMP3(fx)" refers to protein sequences encoded by the human BMP3 gene and defining the conserved seven cysteine skeleton (Seq. ID No. 26). The amino acid sequence for the full length protein appears in Wozney et al. (1988) Science 242: 1528-1534. The pro domain likely extends from the signal peptide cleavage site to residue 290; the

mature protein likely is defined by
residues 291-472.

5 "BMP5(fx)" refers to protein sequences encoded by the
human BMP5 gene and defining the conserved
seven cysteine skeleton (Seq. ID No. 27).
The amino acid sequence for the full
length protein appears in Celeste, et al.
10 (1991) PNAS 87: 9843-9847. The pro domain
likely extends from the signal peptide
cleavage site to residue 316; the mature
protein likely is defined by residues
317-454.

15 "BMP6(fx)" refers to protein sequences encoded by the
human BMP6 gene and defining the conserved
seven cysteine skeleton (Seq. ID No. 28).
The amino acid sequence for the full
length protein appears in Celeste, et al.
20 (1990) PNAS 87: 9843-5847. The pro domain
likely includes extends from the signal
peptide cleavage site to residue 374; the
mature sequence likely includes
residues 375-513.

25

The OP-2 proteins have an additional cysteine
residue in this region (e.g., see residue 41 of Seq. ID
Nos. 7 and 8), in addition to the conserved cysteine
30 skeleton in common with the other proteins in this
family. The GDF-1 protein has a four amino acid insert
within the conserved skeleton (residues 44-47 of Seq.
ID No. 14) but this insert likely does not interfere
with the relationship of the cysteines in the folded
35 structure. In addition, the CBMP2 proteins are missing
one amino acid residue within the cysteine skeleton.

The morphogens are inactive when reduced, but are active as oxidized homodimers and when oxidized in combination with other morphogens of this invention (e.g., asheterodimers). Thus, as defined herein, a morphogen is a dimeric protein comprising a pair of polypeptide chains, wherein each polypeptide chain comprises at least the C-terminal six cysteine skeleton defined by residues 43-139 of Seq. ID No. 5, including functionally equivalent arrangements of these cysteines (e.g., amino acid insertions or deletions which alter the linear arrangement of the cysteines in the sequence but not their relationship in the folded structure), such that, when the polypeptide chains are folded, the dimeric protein species comprising the pair of polypeptide chains has the appropriate three-dimensional structure, including the appropriate intra- or inter-chain disulfide bonds such that the protein is capable of acting as a morphogen as defined herein. Specifically, the morphogens generally are capable of all of the following biological functions in a morphogenically permissive environment: stimulating proliferation of progenitor cells; stimulating the differentiation of progenitor cells; stimulating the proliferation of differentiated cells; and supporting the growth and maintenance of differentiated cells, including the "redifferentiation" of transformed cells. In addition, it is also anticipated that these morphogens are capable of inducing redifferentiation of committed cells under appropriate environmental conditions.

In one preferred aspect, the morphogens of this invention comprise one of two species of generic amino acid sequences: Generic Sequence 1 (Seq. ID No. 1) or

Generic Sequence 2 (Seq. ID No. 2); where each Xaa indicates one of the 20 naturally-occurring L-isomer, α -amino acids or a derivative thereof. Generic Sequence 1 comprises the conserved six cysteine skeleton and Generic Sequence 2 comprises the conserved six cysteine skeleton plus the additional cysteine identified in OP-2 (see residue 36, Seq. ID No. 2). In another preferred aspect, these sequences further comprise the following additional sequence at their N-terminus:

Cys Xaa Xaa Xaa Xaa (Seq. ID No. 15)
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Preferred amino acid sequences within the foregoing generic sequences include: Generic Sequence 3 (Seq. ID No. 3), Generic Sequence 4 (Seq. ID No. 4), Generic Sequence 5 (Seq. ID No. 30) and Generic Sequence 6 (Seq. ID No. 31), listed below. These Generic Sequences accommodate the homologies shared among the various preferred members of this morphogen family identified in Table II, as well as the amino acid sequence variation among them. Specifically, Generic Sequences 3 and 4 are composite amino acid sequences of the following proteins presented in Table II and identified in Seq. ID Nos. 5-14: human OP-1 (hOP-1, Seq. ID Nos. 5 and 16-17), mouse OP-1 (mOP-1, Seq. ID Nos. 6 and 18-19), human and mouse OP-2 (Seq. ID Nos. 7, 8, and 20-22), CBMP2A (Seq. ID No. 9), CBMP2B (Seq. ID No. 10), DPP (from Drosophila, Seq. ID No. 11), Vgl, (from Xenopus, Seq. ID No. 12), Vgr-1 (from mouse, Seq. ID No. 13), and GDF-1 (from mouse, Seq. ID No. 14.) The generic sequences include both the amino acid identity shared by the sequences in Table II, as well as alternative residues for the

variable positions within the sequence. Note that these generic sequences allow for an additional cysteine at position 41 or 46 in Generic Sequences 3 or 4, respectively, providing an appropriate cysteine skeleton where inter- or intramolecular disulfide bonds can form, and contain certain critical amino acids which influence the tertiary structure of the proteins.

Generic Sequence 3

Leu Tyr Val Xaa Phe

1

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Xaa Xaa Xaa Gly Trp Xaa Xaa Trp Xaa

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Xaa Ala Pro Xaa Gly Xaa Xaa Ala

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Xaa Tyr Cys Xaa Gly Xaa Cys Xaa

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Xaa Pro Xaa Xaa Xaa Xaa Xaa

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Xaa Xaa Xaa Asn His Ala Xaa Xaa

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Xaa Xaa Leu Xaa Xaa Xaa Xaa Xaa

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Xaa Xaa Xaa Xaa Xaa Xaa Xaa Cys

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60

Cys Xaa Pro Xaa Xaa Xaa Xaa Xaa

65

Xaa Xaa Xaa Leu Xaa Xaa Xaa

70

75

Xaa Xaa Xaa Xaa Val Xaa Leu Xaa

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Xaa Xaa Xaa Xaa Met Xaa Val Xaa

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Xaa Cys Gly Cys Xaa

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wherein each Xaa is independently selected from a group
of one or more specified amino acids defined as

10 follows: "Res." means "residue" and Xaa at res.4 =
25 (Ser, Asp or Glu); Xaa at res.6 = (Arg, Gln, Ser or
Lys); Xaa at res.7 = (Asp or Glu); Xaa at res.8 = (Leu
or Val); Xaa at res.11 = (Gln, Leu, Asp, His or Asn);
15 Xaa at res.12 = (Asp, Arg or Asn); Xaa at res.14 = (Ile
or Val); Xaa at res.15 = (Ile or Val); Xaa at res.18 =
20 (Glu, Gln, Leu, Lys, Pro or Arg); Xaa at res.20 = (Tyr
or Phe); Xaa at res.21 = (Ala, Ser, Asp, Met, His, Leu
or Gln); Xaa at res.23 = (Tyr, Asn or Phe); Xaa at
res.26 = (Glu, His, Tyr, Asp or Gln); Xaa at res.28 =
25 (Glu, Lys, Asp or Gln); Xaa at res.30 = (Ala, Ser, Pro
or Gln); Xaa at res.31 = (Phe, Leu or Tyr); Xaa at
res.33 = (Leu or Val); Xaa at res.34 = (Asn, Asp, Ala
or Thr); Xaa at res.35 = (Ser, Asp, Glu, Leu or Ala);
Xaa at res.36 = (Tyr, Cys, His, Ser or Ile); Xaa at
30 res.37 = (Met, Phe, Gly or Leu); Xaa at res.38 = (Asn
or Ser); Xaa at res.39 = (Ala, Ser or Gly); Xaa at
res.40 = (Thr, Leu or Ser); Xaa at res.44 = (Ile or
Val); Xaa at res.45 = (Val or Leu); Xaa at res.46 =
(Gln or Arg); Xaa at res.47 = (Thr, Ala or Ser); Xaa at
res.49 = (Val or Met); Xaa at res.50 = (His or Asn);
Xaa at res.51 = (Phe, Leu, Asn, Ser, Ala or Val); Xaa
at res.52 = (Ile, Met, Asn, Ala or Val); Xaa at res.53
= (Asn, Lys, Ala or Glu); Xaa at res.54 = (Pro or Ser);

Xaa at res.55 = (Glu, Asp, Asn, or Gly); Xaa at res.56
 = (Thr, Ala, Val, Lys, Asp, Tyr, Ser or Ala); Xaa at
 res.57 = (Val, Ala or Ile); Xaa at res.58 = (Pro or
 Asp); Xaa at res.59 = (Lys or Leu); Xaa at res.60 =
 5 (Pro or Ala); Xaa at res.63 = (Ala or Val); Xaa at
 res.65 = (Thr or Ala); Xaa at res.66 = (Gln, Lys, Arg
 or Glu); Xaa at res.67 = (Leu, Met or Val); Xaa at
 res.68 = (Asn, Ser or Asp); Xaa at res.69 = (Ala, Pro
 or Ser); Xaa at res.70 = (Ile, Thr or Val); Xaa at
 10 res.71 = (Ser or Ala); Xaa at res.72 = (Val or Met);
 Xaa at res.74 = (Tyr or Phe); Xaa at res.75 = (Phe, Tyr
 or Leu); Xaa at res.76 = (Asp or Asn); Xaa at res.77 =
 (Asp, Glu, Asn or Ser); Xaa at res.78 = (Ser, Gln, Asn
 or Tyr); Xaa at res.79 = (Ser, Asn, Asp or Glu); Xaa at
 15 res.80 = (Asn, Thr or Lys); Xaa at res.82 = (Ile or
 Val); Xaa at res.84 = (Lys or Arg); Xaa at res.85 =
 (Lys, Asn, Gln or His); Xaa at res.86 = (Tyr or His);
 Xaa at res.87 = (Arg, Gln or Glu); Xaa at res.88 =
 (Asn, Glu or Asp); Xaa at res.90 = (Val, Thr or Ala);
 20 Xaa at res.92 = (Arg, Lys, Val, Asp or Glu); Xaa at
 res.93 = (Ala, Gly or Glu); and Xaa at res.97 = (His or
 Arg);

Generic Sequence 4

25 Cys Xaa Xaa Xaa Xaa Leu Tyr Val Xaa Phe
 1 5 10
 Xaa Xaa Xaa Gly Trp Xaa Xaa Trp Xaa
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 30 Xaa Ala Pro Xaa Gly Xaa Xaa Ala
 20 25
 Xaa Tyr Cys Xaa Gly Xaa Cys Xaa
 30 35
 Xaa Pro Xaa Xaa Xaa Xaa Xaa
 35 40

Xaa Xaa Xaa Asn His Ala Xaa Xaa
45 50

Xaa Xaa Leu Xaa Xaa Xaa Xaa Xaa
55

5 Xaa Xaa Xaa Xaa Xaa Xaa Xaa Cys
60 65

Cys Xaa Pro Xaa Xaa Xaa Xaa Xaa
70

Xaa Xaa Xaa Leu Xaa Xaa Xaa
75 80

10 Xaa Xaa Xaa Xaa Val Xaa Leu Xaa
85

Xaa Xaa Xaa Xaa Met Xaa Val Xaa
90 95

15 Xaa Cys Gly Cys Xaa
100

wherein each Xaa is independently selected from a group of one or more specified amino acids as defined by the following: "Res." means "residue" and Xaa at res.2 = (Lys or Arg); Xaa at res.3 = (Lys or Arg); Xaa at res.4 = (His or Arg); Xaa at res.5 = (Glu, Ser, His, Gly, Arg or Pro); Xaa at res.9 = (Ser, Asp or Glu); Xaa at res.11 = (Arg, Gln, Ser or Lys); Xaa at res.12 = (Asp or Glu); Xaa at res.13 = (Leu or Val); Xaa at res.16 = (Gln, Leu, Asp, His or Asn); Xaa at res.17 = (Asp, Arg, or Asn); Xaa at res.19 = (Ile or Val); Xaa at res.20 = (Ile or Val); Xaa at res.23 = (Glu, Gln, Leu, Lys, Pro or Arg); Xaa at res.25 = (Tyr or Phe); Xaa at res.26 = (Ala, Ser, Asp, Met, His, Leu, or Gln); Xaa at res.28 = (Tyr, Asn or Phe); Xaa at res.31 = (Glu, His, Tyr, Asp or Gln); Xaa at res.33 = Glu, Lys, Asp or Gln); Xaa at res.35 = (Ala, Ser or Pro); Xaa at res.36 = (Phe, Leu or Tyr); Xaa at res.38 = (Leu or Val); Xaa at res.39 = (Asn, Asp, Ala or Thr); Xaa at res.40 = (Ser, Asp, Glu, Leu or Ala); Xaa at res.41 = (Tyr, Cys, His, Ser or

Ile); Xaa at res.42 = (Met, Phe, Gly or Leu); Xaa at
res.44 = (Ala, Ser or Gly); Xaa at res.45 = (Thr, Leu
or Ser); Xaa at res.49 = (Ile or Val); Xaa at res.50 =
(Val or Leu); Xaa at res.51 = (Gln or Arg); Xaa at
5 res.52 = (Thr, Ala or Ser); Xaa at res.54 = (Val or
Met); Xaa at res.55 = (His or Asn); Xaa at res.56 =
(Phe, Leu, Asn, Ser, Ala or Val); Xaa at res.57 = (Ile,
Met, Asn, Ala or Val); Xaa at res.58 = (Asn, Lys, Ala
or Glu); Xaa at res.59 = (Pro or Ser); Xaa at res.60 =
10 (Glu, Asp, or Gly); Xaa at res.61 = (Thr, Ala, Val,
Lys, Asp, Tyr, Ser or Ala); Xaa at res.62 = (Val, Ala
or Ile); Xaa at res.63 = (Pro or Asp); Xaa at res.64 =
(Lys or Leu); Xaa at res.65 = (Pro or Ala); Xaa at
res.68 = (Ala or Val); Xaa at res.70 = (Thr or Ala);
15 Xaa at res.71 = (Gln, Lys, Arg or Glu); Xaa at res.72 =
(Leu, Met or Val); Xaa at res.73 = (Asn, Ser or Asp);
Xaa at res.74 = (Ala, Pro or Ser); Xaa at res.75 =
(Ile, Thr or Val); Xaa at res.76 = (Ser or Ala); Xaa at
res.77 = (Val or Met); Xaa at res.79 = (Tyr or Phe);
20 Xaa at res.80 = (Phe, Tyr or Leu); Xaa at res.81 = (Asp
or Asn); Xaa at res.82 = (Asp, Glu, Asn or Ser); Xaa at
res.83 = (Ser, Gln, Asn or Tyr); Xaa at res.84 = (Ser,
Asn, Asp or Glu); Xaa at res.85 = (Asn, Thr or Lys);
Xaa at res.87 = (Ile or Val); Xaa at res.89 = (Lys or
25 Arg); Xaa at res.90 = (Lys, Asn, Gln or His); Xaa at
res.91 = (Tyr or His); Xaa at res.92 = (Arg, Gln or
Glu); Xaa at res.93 = (Asn, Glu or Asp); Xaa at res.95
= (Val, Thr or Ala); Xaa at res.97 = (Arg, Lys, Val,
Asp or Glu); Xaa at res.98 = (Ala, Gly or Glu); and Xaa
30 at res.102 = (His or Arg).

Similarly, Generic Sequence 5 (Seq. ID No. 30) and
Generic Sequence 6 (Seq. ID No. 31) accommodate the
homologies shared among all the morphogen protein
35 family members identified in Table II. Specifically,

25

30

Leu Xaa Xaa Xaa Phe

Xaa Xaa Xaa Gly Trp Xaa Xaa Trp Xaa

Xaa Xaa Pro Xaa Xaa Xaa Xaa Ala

Xaa Tyr Cys Xaa Gly Xaa Cys Xaa

25 30
Xaa Pro Xaa Xaa Xaa Xaa Xaa
35
Xaa Xaa Xaa Asn His Ala Xaa Xaa
40 45
Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
50
Xaa Xaa Xaa Xaa Xaa Xaa Xaa Cys
55 60
Cys Xaa Pro Xaa Xaa Xaa Xaa Xaa
65
Xaa Xaa Xaa Leu Xaa Xaa Xaa
70 75
Xaa Xaa Xaa Xaa Val Xaa Leu Xaa
80
Xaa Xaa Xaa Xaa Met Xaa Val Xaa
85 90
Xaa Cys Xaa Cys Xaa
95

20 wherein each Xaa is independently selected from a group
of one or more specified amino acids defined as
follows: "Res." means "residue" and Xaa at res.2 =
(Tyr or Lys); Xaa at res.3 = Val or Ile); Xaa at res.4
= (Ser, Asp or Glu); Xaa at res.6 = (Arg, Gln, Ser, Lys
25 or Ala); Xaa at res.7 = (Asp, Glu or Lys); Xaa at res.8
= (Leu, Val or Ile); Xaa at res.11 = (Gln, Leu, Asp,
His, Asn or Ser); Xaa at res.12 = (Asp, Arg, Asn or
Glu); Xaa at res.14 = (Ile or Val); Xaa at res.15 =
(Ile or Val); Xaa at res.16 (Ala or Ser); Xaa at res.18

= (Glu, Gln, Leu, Lys, Pro or Arg); Xaa at res.19 =
(Gly or Ser); Xaa at res.20 = (Tyr or Phe); Xaa at
res.21 = (Ala, Ser, Asp, Met, His, Gln, Leu or Gly);
Xaa at res.23 = (Tyr, Asn or Phe); Xaa at res.26 =
5 (Glu, His, Tyr, Asp, Gln or Ser); Xaa at res.28 = (Glu,
Lys, Asp, Gln or Ala); Xaa at res.30 = (Ala, Ser, Pro,
Gln or Asn); Xaa at res.31 = (Phe, Leu or Tyr); Xaa at
res.33 = (Leu, Val or Met); Xaa at res.34 = (Asn, Asp,
Ala, Thr or Pro); Xaa at res.35 = (Ser, Asp, Glu, Leu,
10 Ala or Lys); Xaa at res.36 = (Tyr, Cys, His, Ser or
Ile); Xaa at res.37 = (Met, Phe, Gly or Leu); Xaa at
res.38 = (Asn, Ser or Lys); Xaa at res.39 = (Ala, Ser,
Gly or Pro); Xaa at res.40 = (Thr, Leu or Ser); Xaa at
res.44 = (Ile, Val or Thr); Xaa at res.45 = (Val, Leu
15 or Ile); Xaa at res.46 = (Gln or Arg); Xaa at res.47 =
(Thr, Ala or Ser); Xaa at res.48 = (Leu or Ile); Xaa at
res.49 = (Val or Met); Xaa at res.50 = (His, Asn or
Arg); Xaa at res.51 = (Phe, Leu, Asn, Ser, Ala or Val);
Xaa at res.52 = (Ile, Met, Asn, Ala, Val or Leu); Xaa
20 at res.53 = (Asn, Lys, Ala, Glu, Gly or Phe); Xaa at
res.54 = (Pro, Ser or Val); Xaa at res.55 = (Glu, Asp,
Asn, Gly, Val or Lys); Xaa at res.56 = (Thr, Ala, Val,
Lys, Asp, Tyr, Ser, Ala, Pro or His); Xaa at res.57 =
(Val, Ala or Ile); Xaa at res.58 = (Pro or Asp); Xaa at
25 res.59 = (Lys, Leu or Glu); Xaa at res.60 = (Pro or
Ala); Xaa at res.63 = (Ala or Val); Xaa at res.65 =
(Thr, Ala or Glu); Xaa at res.66 = (Gln, Lys, Arg or
Glu); Xaa at res.67 = (Leu, Met or Val); Xaa at res.68
= (Asn, Ser, Asp or Gly); Xaa at res.69 = (Ala, Pro or
30 Ser); Xaa at res.70 = (Ile, Thr, Val or Leu); Xaa at
res.71 = (Ser, Ala or Pro); Xaa at res.72 = (Val, Met
or Ile); Xaa at res.74 = (Tyr or Phe); Xaa at res.75 =
(Phe, Tyr, Leu or His); Xaa at res.76 = (Asp, Asn or
Leu); Xaa at res.77 = (Asp, Glu, Asn or Ser); Xaa at
35 res.78 = (Ser, Gln, Asn, Tyr or Asp); Xaa at res.79 =

(Ser, Asn, Asp, Glu or Lys); Xaa at res.80 = (Asn, Thr or Lys); Xaa at res.82 = (Ile, Val or Asn); Xaa at res.84 = (Lys or Arg); Xaa at res.85 = (Lys, Asn, Gln, His or Val); Xaa at res.86 = (Tyr or His); Xaa at res.87 = (Arg, Gln, Glu or Pro); Xaa at res.88 = (Asn, Glu or Asp); Xaa at res.90 = (Val, Thr, Ala or Ile); Xaa at res.92 = (Arg, Lys, Val, Asp or Glu); Xaa at res.93 = (Ala, Gly, Glu or Ser); Xaa at res.95 = (Gly or Ala) and Xaa at res.97 = (His or Arg).

10

Generic Sequence 6

Cys Xaa Xaa Xaa Xaa Leu Xaa Xaa Xaa Phe

1 5 10

Xaa Xaa Xaa Gly Trp Xaa Xaa Trp Xaa

15

Xaa Xaa Pro Xaa Xaa Xaa Xaa Ala

20

Xaa Tyr Cys Xaa Gly Xaa Cys Xaa

30 35

Xaa Pro Xaa Xaa Xaa Xaa Xaa

40

Xaa Xaa Xaa Asn His Ala Xaa Xaa

45 50

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa

55

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Cys

60 65

Cys Xaa Pro Xaa Xaa Xaa Xaa Xaa

70

Xaa Xaa Xaa Leu Xaa Xaa Xaa

75 80

Xaa Xaa Xaa Xaa Val Xaa Leu Xaa

85

Xaa Xaa Xaa Xaa Met Xaa Val Xaa

90

95

Xaa Cys Xaa Cys Xaa

100

5 wherein each Xaa is independently selected from a group
of one or more specified amino acids as defined by the
following: "Res." means "residue" and Xaa at res.2 =
(Lys, Arg, Ala or Gln); Xaa at res.3 = (Lys, Arg or
Met); Xaa at res.4 = (His, Arg or Gln); Xaa at res.5 =
10 (Glu, Ser, His, Gly, Arg, Pro, Thr, or Tyr); Xaa at
res.7 = (Tyr or Lys); Xaa at res.8 = (Val or Ile); Xaa
at res.9 = (Ser, Asp or Glu); Xaa at res.11 = (Arg,
Gln, Ser, Lys or Ala); Xaa at res.12 = (Asp, Glu, or
Lys); Xaa at res.13 = (Leu, Val or Ile); Xaa at res.16
15 = (Gln, Leu, Asp, His, Asn or Ser); Xaa at res.17 =
(Asp, Arg, Asn or Glu); Xaa at res.19 = (Ile or Val);
Xaa at res.20 = (Ile or Val); Xaa at res.21 = (Ala or
Ser); Xaa at res.23 = (Glu, Gln, Leu, Lys, Pro or Arg);
Xaa at res.24 = (Gly or Ser); Xaa at res.25 = (Tyr or
20 Phe); Xaa at res.26 = (Ala, Ser, Asp, Met, His, Gln,
Leu, or Gly); Xaa at res.28 = (Tyr, Asn or Phe); Xaa at
res.31 = (Glu, His, Tyr, Asp, Gln or Ser); Xaa at
res.33 = Glu, Lys, Asp, Gln or Ala); Xaa at res.35 =
(Ala, Ser, Pro, Gln or Asn); Xaa at res.36 = (Phe, Leu
25 or Tyr); Xaa at res.38 = (Leu, Val or Met); Xaa at
res.39 = (Asn, Asp, Ala, Thr or Pro); Xaa at res.40 =
(Ser, Asp, Glu, Leu, Ala or Lys); Xaa at res.41 = (Tyr,
Cys, His, Ser or Ile); Xaa at res.42 = (Met, Phe, Gly
or Leu); Xaa at res.43 = (Asn, Ser or Lys); Xaa at
30 res.44 = (Ala, Ser, Gly or Pro); Xaa at res.45 = (Thr,
Leu or Ser); Xaa at res.49 = (Ile, Val or Thr); Xaa at
res.50 = (Val, Leu or Ile); Xaa at res.51 = (Gln or
Arg); Xaa at res.52 = (Thr, Ala or Ser); Xaa at res.53
= (Leu or Ile); Xaa at res.54 = (Val or Met); Xaa at
35 res.55 = (His, Asn or Arg); Xaa at res.56 = (Phe, Leu,

Asn, Ser, Ala or Val); Xaa at res.57 = (Ile, Met, Asn, Ala, Val or Leu); Xaa at res.58 = (Asn, Lys, Ala, Glu, Gly or Phe); Xaa at res.59 = (Pro, Ser or Val); Xaa at res.60 = (Glu, Asp, Gly, Val or Lys); Xaa at res.61 =
5 (Thr, Ala, Val, Lys, Asp, Tyr, Ser, Ala, Pro or His); Xaa at res.62 = (Val, Ala or Ile); Xaa at res.63 = (Pro or Asp); Xaa at res.64 = (Lys, Leu or Glu); Xaa at res.65 = (Pro or Ala); Xaa at res.68 = (Ala or Val); Xaa at res.70 = (Thr, Ala or Glu); Xaa at res.71 =
10 (Gln, Lys, Arg or Glu); Xaa at res.72 = (Leu, Met or Val); Xaa at res.73 = (Asn, Ser, Asp or Gly); Xaa at res.74 = (Ala, Pro or Ser); Xaa at res.75 = (Ile, Thr, Val or Leu); Xaa at res.76 = (Ser, Ala or Pro); Xaa at res.77 = (Val, Met or Ile); Xaa at res.79 = (Tyr or
15 Phe); Xaa at res.80 = (Phe, Tyr, Leu or His); Xaa at res.81 = (Asp, Asn or Leu); Xaa at res.82 = (Asp, Glu, Asn or Ser); Xaa at res.83 = (Ser, Gln, Asn, Tyr or Asp); Xaa at res.84 = (Ser, Asn, Asp, Glu or Lys); Xaa at res.85 = (Asn, Thr or Lys); Xaa at res.87 = (Ile,
20 Val or Asn); Xaa at res.89 = (Lys or Arg); Xaa at res.90 = (Lys, Asn, Gln, His or Val); Xaa at res.91 = (Tyr or His); Xaa at res.92 = (Arg, Gln, Glu or Pro); Xaa at res.93 = (Asn, Glu or Asp); Xaa at res.95 = (Val, Thr, Ala or Ile); Xaa at res.97 = (Arg, Lys, Val,
25 Asp or Glu); Xaa at res.98 = (Ala, Gly, Glu or Ser); Xaa at res.100 = (Gly or Ala); and Xaa at res.102 = (His or Arg).

Particularly useful sequences for use as morphogens
30 in this invention include the C-terminal domains, e.g., the C-terminal 96-102 amino acid residues of Vgl, Vgr-1, DPP, OP-1, OP-2, CBMP-2A, CBMP-2B, GDF-1 (see Table II, below, and Seq. ID Nos. 5-14), as well as proteins comprising the C-terminal domains of 60A,
35 BMP3, BMP5 and BMP6 (see Seq. ID Nos. 24-28), all of

which include at least the conserved six or seven cysteine skeleton. In addition, biosynthetic constructs designed from the generic sequences, such as COP-1, 3-5, 7, 16, disclosed in U.S. Pat. No.

5 5,011,691, also are useful. Other sequences include the inhibins/activin proteins (see, for example, U.S. Pat. Nos. 4,968,590 and 5,011,691). Accordingly, other useful sequences are those sharing at least 70% amino acid sequence homology or "similarity", and preferably
10 80% homology or similarity with any of the sequences above. These are anticipated to include allelic and species variants and mutants, and biosynthetic muteins, as well as novel members of this morphogenic family of proteins. Particularly envisioned in the family of
15 related proteins are those proteins exhibiting morphogenic activity and wherein the amino acid changes from the preferred sequences include conservative changes, e.g., those as defined by Dayoff et al., Atlas of Protein Sequence and Structure; vol. 5, Suppl. 3,
20 pp. 345-362, (M.O. Dayoff, ed., Nat'l BioMed. Research Fdn., Washington, D.C. 1979). As used herein, potentially useful sequences are aligned with a known morphogen sequence using the method of Needleman et al. ((1970) J.Mol.Biol. 48:443-453) and identities
25 calculated by the Align program (DNASTar, Inc.). "Homology" or "similarity" as used herein includes allowed conservative changes as defined by Dayoff et al.

30 The currently most preferred protein sequences useful as morphogens in this invention include those having greater than 60% identity, preferably greater than 65% identity, with the amino acid sequence defining the conserved six cysteine skeleton of hOP1
35 (e.g., residues 43-139 of Seq. ID No. 5). These most

preferred sequences include both allelic and species variants of the OP-1 and OP-2 proteins, including the Drosophila 60A protein. Accordingly, in another preferred aspect of the invention, useful morphogens include active proteins comprising species of polypeptide chains having the generic amino acid sequence herein referred to as "OPX", which accommodates the homologies between the various identified species of OP1 and OP2 (Seq. ID No. 29).

The morphogens useful in the methods, composition and devices of this invention include proteins comprising any of the polypeptide chains described above, whether isolated from naturally-occurring sources, or produced by recombinant DNA or other synthetic techniques, and includes allelic and species variants of these proteins, naturally-occurring or biosynthetic mutants thereof, as well as various truncated and fusion constructs. Deletion or addition mutants also are envisioned to be active, including those which may alter the conserved C-terminal cysteine skeleton, provided that the alteration does not functionally disrupt the relationship of these cysteines in the folded structure. Accordingly, such active forms are considered the equivalent of the specifically described constructs disclosed herein. The proteins may include forms having varying glycosylation patterns, varying N-termini, a family of related proteins having regions of amino acid sequence homology, and active truncated or mutated forms of native or biosynthetic proteins, produced by expression of recombinant DNA in host cells.

The morphogenic proteins can be expressed from intact or truncated cDNA or from synthetic DNAs in

procaryotic or eucaryotic host cells, and purified, cleaved, refolded, and dimerized to form morphogenically active compositions. Currently preferred host cells include E. coli or mammalian cells, such as CHO, COS or BSC cells. A detailed description of the morphogens useful in the methods, compositions and devices of this invention is disclosed in copending US patent application Serial Nos. 752,764, filed August 30, 1991, and 667,274, filed March 11, 1991, the disclosure of which are incorporated herein by reference.

Thus, in view of this disclosure, skilled genetic engineers can isolate genes from cDNA or genomic libraries of various different species which encode appropriate amino acid sequences, or construct DNAs from oligonucleotides, and then can express them in various types of host cells, including both procaryotes and eucaryotes, to produce large quantities of active proteins capable of protecting tissues and organs from immune cell-mediated tissue destruction, including substantially inhibiting such damage and/or regenerating the damaged tissue in a variety of mammals, including humans.

The foregoing and other objects, features and advantages of the present invention will be made more apparent from the following detailed description of the invention.

Brief Description of the Drawings

FIG 1 shows the cardioprotective effects of morphogen (hOP1) in a rat myocardial ischemia-reperfusion model, as evidenced by the smaller loss of myocardial creatine kinase in hOP1-treated rats;

FIG 2 shows the effects of 20 μ g of morphogen (hOP1) given 24 hours prior to isolation of rat heart on endothelial-dependent vasorelaxation to acetylcholine following induced ischemia-reperfusion injury;

FIG 3 shows the effect of morphogen (hOP1) on neutrophil adherence to LTB₄-stimulated mesenteric artery endothelium in neutrophil-activated rats;

FIG 4 (A and B) are schematic representations of morphogen inhibition of early mononuclear phagocytic multinuclearization in vivo;

FIG 5 graphs the effect of a morphogen (e.g., OP-1) and a placebo control on mucositis lesion formation; and

FIG 6 (A-D) graphs the effects of a morphogen (eg., OP-1, Figs. 6A and 6C) and TGF- β (Fig. 6B and 6D) on collagen (6A and 6B) and hyaluronic acid (6C and 6D) production in primary fibroblast cultures.

Detailed Description of the Invention

It now has been surprisingly discovered that the morphogens defined herein are effective agents in alleviating the tissue destructive effects associated with the body's inflammatory response to tissue injury. In particular, as disclosed herein, the morphogens are capable of alleviating the necrotic tissue effects associated with the ensuing inflammatory responses that occur following an initial tissue injury.

When tissue injury occurs, whether caused by bacteria, trauma, chemicals, heat, or any other phenomenon, the body's inflammatory response is stimulated. In response to signals released from the damaged cells (e.g., cytokines), extravascularization of immune effector cells is induced. Under ordinary circumstances these invading immune effector cells kill the infectious agent and/or infected or damaged cells (through the release of killing substances such as superoxides, perforins, and other antimicrobial agents stored in granules), remove the dead tissues and organisms (through phagocytosis), release various biological response modifiers that promote rapid healing and covering of the wound (quite often resulting in the formation of fibrotic scar tissue), and then, after the area is successfully healed, exit from the site of the initial insult. Once the site is perceived to be normal, the local release of inflammatory cytokines ceases and the display of adhesion molecules on the vessel endothelium returns to basal levels. In some cases, however, the zeal of these interacting signals and cellular systems, which are designed to capture and contain very rapidly multiplying infectious agents, act to the detriment of

the body, killing additional, otherwise healthy, surrounding tissue. This additional unnecessary tissue death further compromises organ function and sometimes results in death of the individual. In addition, the resulting scar tissue that often forms can interfere with normal tissue function as occurs, for example, in idiopathic pulmonary fibrosis, IBD and organ cirrhosis.

The vascular endothelium constitutes the first barrier between circulating immune effector cells and extravascular tissues. Extravasation of these circulating cells requires that they bind to the vascular endothelial cells, cross the basement membrane, and enter insulted tissues e.g., by phagocytosis or protease-mediated extracellular matrix degradation. Without being limited to a particular theory, it is believed that the morphogens of this invention may modulate the inflammatory response in part by modulating the attachment of immune effector cells to the luminal side of the endothelium of blood vessels at or near sites of tissue damage and/or inflammatory lesions. Because the method reduces or prevents the attachment of immune effector cells at these sites, it also prevents the subsequent release of tissue destructive agents by these same immune effector cells at sites of tissue damage and/or inflammatory lesions. Because attachment of immune effector cells to the endothelium must precede their extravascularization, the method also prevents the initial or continued entry of these cells into extravascular sites of tissue destruction or ongoing inflammatory lesions. Therefore, the invention not only relates to a method to reduce or prevent the immune cell-mediated cellular destruction at extravascular sites of recent tissue destruction, but

also relates to a method to prevent or reduce the continued entry of immune effector cells into extravascular sites of ongoing inflammatory cascades. As will be appreciated by those skilled in the art, the morphogens of this invention also may be contemplated in mechanisms for disrupting the functional interaction of immune effector cells with endothelium where the adhesion molecules are induced by means other than in response to tissue injury.

10

One source of tissue damage follows cell exposure to toxic oxygen concentrations, such as the tissue damage following ischemic-reperfusion tissue injury (oxygen deprivation), and following hyperoxia injury (lethally high oxygen concentrations). Accordingly, the process of the present invention provides a method for alleviating the tissue damage induced by ischemic-reperfusion injury or hyperoxia-induced injury comprising the step of administering to the afflicted individual a therapeutic amount of a morphogen prior to, during, or after damage to the affected tissue. Where the toxic oxygen concentrations may be deliberately or unavoidably induced, as by a surgical or clinical procedure, the morphogen preferably is administered prior to induction.

In addition, the morphogens described herein, in contrast to fibrogenic growth factors such as TGF- β , stimulate tissue morphogenesis and do not stimulate fibrosis or scar tissue formation (see Example 9, below.) Accordingly, in addition to inhibiting the tissue destructive effects associated with the inflammatory response, the morphogens further enhance the viability of damaged tissue and/or organs by stimulating the regeneration of the damaged tissue and preventing fibrogenesis.

The morphogens described herein also can inhibit epithelial cell proliferation (see Example 10, below.) This activity of the morphogens also may be particularly useful in the treatment of psoriasis and other inflammatory diseases that involve epithelial cell populations.

Provided below are detailed descriptions of suitable morphogens useful in the methods and compositions of this invention, as well as methods for their administration and application, and numerous, nonlimiting examples which 1) illustrate the suitability of the morphogens and morphogen-stimulating agents described herein as therapeutic agents for protecting tissue from the tissue destructive effects associated with the body's inflammatory response; and 2) provide assays with which to test candidate morphogens and morphogen-stimulating agents for their efficacy.

I. Useful Morphogens

As defined herein a protein is morphogenic if it is capable of inducing the developmental cascade of cellular and molecular events that culminate in the formation of new, organ-specific tissue and comprises at least the conserved C-terminal six cysteine skeleton or its functional equivalent (see supra). Specifically, the morphogens generally are capable of all of the following biological functions in a morphogenically permissive environment: stimulating proliferation of progenitor cells; stimulating the differentiation of progenitor cells; stimulating the

proliferation of differentiated cells; and supporting the growth and maintenance of differentiated cells, including the "redifferentiation" of transformed cells. Details of how the morphogens useful in the method of this invention first were identified, as well as a description on how to make, use and test them for morphogenic activity are disclosed in USSN 667,274, filed March 11, 1991 and USSN 752,764, filed August 30, 1991, the disclosures of which are hereinabove incorporated by reference. As disclosed therein, the morphogens may be purified from naturally-sourced material or recombinantly produced from procaryotic or eucaryotic host cells, using the genetic sequences disclosed therein. Alternatively, novel morphogenic sequences may be identified following the procedures disclosed therein.

Particularly useful proteins include those which comprise the naturally derived sequences disclosed in Table II. Other useful sequences include biosynthetic constructs such as those disclosed in U.S. Pat. 5,011,691, the disclosure of which is incorporated herein by reference (e.g., COP-1, COP-3, COP-4, COP-5, COP-7, and COP-16).

Accordingly, the morphogens useful in the methods and compositions of this invention also may be described by morphogenically active proteins having amino acid sequences sharing 70% or, preferably, 80% homology (similarity) with any of the sequences described above, where "homology" is as defined herein above.

The morphogens useful in the method of this invention also can be described by any of the 6 generic

sequences described herein (Generic Sequences 1, 2, 3, 4, 5 and 6). Generic sequences 1 and 2 also may include, at their N-terminus, the sequence

5 Cys Xaa Xaa Xaa Xaa (Seq. ID No. 15)
 1 5

Table II, set forth below, compares the amino acid sequences of the active regions of native proteins that have been identified as morphogens, including human OP-1 (hOP-1, Seq. ID Nos. 5 and 16-17), mouse OP-1 (mOP-1, Seq. ID Nos. 6 and 18-19), human and mouse OP-2 (Seq. ID Nos. 7, 8, and 20-23), CBMP2A (Seq. ID No. 9), CBMP2B (Seq. ID No. 10), BMP3 (Seq. ID No. 26), DPP (from Drosophila, Seq. ID No. 11), Vgl, (from Xenopus, Seq. ID No. 12), Vgr-1 (from mouse, Seq. ID No. 13), GDF-1 (from mouse, Seq. ID Nos. 14, 32 and 33), 60A protein (from Drosophila, Seq. ID Nos. 24 and 25), BMP5 (Seq. ID No. 27) and BMP6 (Seq. ID No. 28). The sequences are aligned essentially following the method of Needleman et al. (1970) J. Mol. Biol., 48:443-453, calculated using the Align Program (DNASTar, Inc.) In the table, three dots indicates that the amino acid in that position is the same as the amino acid in hOP-1. Three dashes indicates that no amino acid is present in that position, and are included for purposes of illustrating homologies. For example, amino acid residue 60 of CBMP-2A and CBMP-2B is "missing". Of course, both these amino acid sequences in this region comprise Asn-Ser (residues 58, 59), with CBMP-2A then comprising Lys and Ile, whereas CBMP-2B comprises Ser and Ile.

5	DPP	...	Asn	Asn	Asn	Gly	Lys	...		
	Vgl	Ser	...	Glu	Asp	Ile		
	Vgr-1	Val	Met	Tyr	...		
	CBMP-2A	...	Asn	Ser	Val	...	Ser	---	Lys	Ile		
	CBMP-2B	...	Asn	Ser	Val	...	Ser	---	Ser	Ile		
	BMP3	...	Arg	Ala**	Gly	Val	Val	Pro	Gly	Ile		
	GDF-1	Met	...	Ala	Ala	Ala	...	Gly	Ala	Ala		
	60A	Leu	Leu	Glu	...	Lys	Lys	...		
10	BMP5	Leu	Met	Phe	...	Asp	His	...		
	BMP6	Leu	Met	Tyr	...		
			55								60	
15	hOP-1	Pro	Lys	Pro	Cys	Cys	Ala	Pro	Thr	Gln		
	mOP-1		
	hOP-2	Ala	Lys		
	mOP-2	Ala	Lys		
	DPP	Ala	Val		
	Vgl	...	Leu	Val	Lys		
	Vgr-1	Lys		
	CBMP-2A	Ala	Val	Glu		
20	CBMP-2B	Ala	Val	Glu		
	BMP3	...	Glu	Val	...	Glu	Lys		
	GDF-1	Asp	Leu	Val	...	Ala	Arg		
	60A	Arg		
	BMP5	Lys		
	BMP6	Lys		
				65								70
	30	hOP-1	Leu	Asn	Ala	Ile	Ser	Val	Leu	Tyr	Phe	
mOP-1			
hOP-2		...	Ser	...	Thr	Tyr		
mOP-2		...	Ser	...	Thr	Tyr		
Vgl		Met	Ser	Pro	Met	...	Phe	Tyr		
35	Vgr-1	Val		

	DPP	...	Asp	Ser	Val	Ala	Met	Leu
	CBMP-2A	...	Ser	Met	Leu
	CBMP-2B	...	Ser	Met	Leu
	BMP3	Met	Ser	Ser	Leu	...	Ile	...	Phe	Tyr
5	GDF-1	...	Ser	Pro	Phe	...
	60A	...	Gly	...	Leu	Pro	His
	BMP5
	BMP6
					75					80
10	hOP-1	Asp	Asp	Ser	Ser	Asn	Val	Ile	Leu	Lys
	mOP-1
	hOP-2	...	Ser	...	Asn	Arg
	mOP-2	...	Ser	...	Asn	Arg
15	DPP	Asn	...	Gln	...	Thr	...	Val
	Vgl	...	Asn	Asn	Asp	Val	...	Arg
	Vgr-1	Asn
	CBMP-2A	...	Glu	Asn	Glu	Lys	...	Val
	CBMP-2B	...	Glu	Tyr	Asp	Lys	...	Val
20	BMP3	...	Glu	Asn	Lys	Val
	GDF-1	...	Asn	...	Asp	Val	...	Arg
	60A	Leu	Asn	Asp	Glu	Asn
	BMP5
	BMP6	Asn
25						85				
	hOP-1	Lys	Tyr	Arg	Asn	Met	Val	Val	Arg	
	mOP-1	
30	hOP-2	...	His	Lys	
	mOP-2	...	His	Lys	
	DPP	Asn	...	Gln	Glu	...	Thr	...	Val	
	Vgl	His	...	Glu	Ala	...	Asp	
	Vgr-1	
35	CBMP-2A	Asn	...	Gln	Asp	Glu	

	CBMP-2B	Asn	...	Gln	Glu	Glu
	BMP3	Val	...	Pro	Thr	...	Glu
	GDF-1	Gln	...	Glu	Asp	Asp
	60A	Ile	...	Lys
5	BMP5
	BMP6	Trp
		90					95		

10	hOP-1	Ala	Cys	Gly	Cys	His
	mOP-1
	hOP-2
	mOP-2
	DPP	Gly	Arg
15	Vgl	Glu	Arg
	Vgr-1
	CBMP-2A	Gly	Arg
	CBMP-2B	Gly	Arg
	BMP3	Ser	...	Ala	...	Arg
20	GDF-1	Glu	Arg
	60A	Ser
	BMP5	Ser
	BMP6
				100		

25 **Between residues 56 and 57 of BMP3 is a Val residue;
 between residues 43 and 44 of GDF-1 lies
 the amino acid sequence Gly-Gly-Pro-Pro.

30 As is apparent from the foregoing amino acid
 sequence comparisons, significant amino acid changes
 can be made within the generic sequences while
 retaining the morphogenic activity. For example, while
 the GDF-1 protein sequence depicted in Table II shares
 only about 50% amino acid identity with the hOP1

35

sequence described therein, the GDF-1 sequence shares greater than 70% amino acid sequence homology (or "similarity") with the hOP1 sequence, where "homology" or "similarity" includes allowed conservative amino acid changes within the sequence as defined by Dayoff, et al., Atlas of Protein Sequence and Structure vol.5, supp.3, pp.345-362, (M.O. Dayoff, ed., Nat'l BioMed. Res. Fd'n, Washington D.C. 1979.)

10 The currently most preferred protein sequences useful as morphogens in this invention include those having greater than 60% identity, preferably greater than 65% identity, with the amino acid sequence defining the conserved six cysteine skeleton of hOP1 (e.g., residues 43-139 of Seq. ID No. 5). These most preferred sequences include both allelic and species variants of the OP-1 and OP-2 proteins, including the Drosophila 60A protein. Accordingly, in still another preferred aspect, the invention includes morphogens comprising species of polypeptide chains having the generic amino acid sequence referred to herein as "OPX", which defines the seven cysteine skeleton and accommodates the identities between the various identified mouse and human OP1 and OP2 proteins. OPX is presented in Seq. ID No. 29. As described therein, each Xaa at a given position independently is selected from the residues occurring at the corresponding position in the C-terminal sequence of mouse or human OP1 or OP2 (see Seq. ID Nos. 5-8 and/or Seq. ID Nos. 16-23).

II. Formulations and Methods for Administering Therapeutic Agents

The morphogens may be provided to an individual by

any suitable means, preferably directly (e.g., locally, as by injection or topical administration to a tissue locus) or systemically (e.g., parenterally or orally). Where the morphogen is to be provided parenterally, such as by intravenous, subcutaneous, intramuscular, intraorbital, ophthalmic, intraventricular, intracranial, intracapsular, intraspinal, intracisternal, intraperitoneal, buccal, rectal, vaginal, intranasal or by aerosol administration, the morphogen preferably comprises part of an aqueous solution. The solution is physiologically acceptable so that in addition to delivery of the desired morphogen to the patient, the solution does not otherwise adversely affect the patient's electrolyte and volume balance. The aqueous medium for the morphogen thus may comprise normal physiologic saline (9.85% NaCl, 0.15M), pH 7-7.4. The aqueous solution containing the morphogen can be made, for example, by dissolving the protein in 50% ethanol containing acetonitrile in 0.1% trifluoroacetic acid (TFA) or 0.1% HCl, or equivalent solvents. One volume of the resultant solution then is added, for example, to ten volumes of phosphate buffered saline (PBS), which further may include 0.1-0.2% human serum albumin (HSA). The resultant solution preferably is vortexed extensively. If desired, a given morphogen may be made more soluble by association with a suitable molecule. For example, association of the mature dimer with the pro domain of the morphogen keeps the morphogen soluble in physiological buffers. In fact, the endogenous protein is thought to be transported in this form. Another molecule capable of enhancing solubility and particularly useful for oral administrations, is casein. For example, addition of 0.2% casein increases solubility of the mature active form of OP-1 by 80%.

Other components found in milk and/or various serum proteins also may be useful.

Useful solutions for parenteral administration may
5 be prepared by any of the methods well known in the
pharmaceutical art, described, for example, in
Remington's Pharmaceutical Sciences (Gennaro, A., ed.),
Mack Pub., 1990. Formulations may include, for
example, polyalkylene glycols such as polyethylene
10 glycol, oils of vegetable origin, hydrogenated
naphthalenes, and the like. Formulations for direct
administration, in particular, may include glycerol and
other compositions of high viscosity to help maintain
the morphogen at the desired locus. Biocompatible,
15 preferably bioresorbable, polymers, including, for
example, hyaluronic acid, collagen, tricalcium
phosphate, polybutyrate, lactide, and glycolide
polymers and lactide/glycolide copolymers, may be
useful excipients to control the release of the
20 morphogen in vivo. Other potentially useful parenteral
delivery systems for these morphogens include ethylene-
vinyl acetate copolymer particles, osmotic pumps,
implantable infusion systems, and liposomes.
Formulations for inhalation administration contain as
25 excipients, for example, lactose, or may be aqueous
solutions containing, for example, polyoxyethylene-9-
lauryl ether, glycocholate and deoxycholate, or oily
solutions for administration in the form of nasal
drops, or as a gel to be applied intranasally.
30 Formulations for parenteral administration may also
include glycocholate for buccal administration,
methoxysalicylate for rectal administration, or cutric
acid for vaginal administration.

Suppositories for rectal administration also may be prepared by mixing the morphogen or morphogen-stimulating agent with a non-irritating excipient such as cocoa butter or other compositions which are solid at room temperature and liquid at body temperatures.

Formulations for topical administration to the skin surface may be prepared by dispersing the morphogen or morphogen-stimulating agent with a dermatologically acceptable carrier such as a lotion, cream, ointment or soap. Particularly useful are carriers capable of forming a film or layer over the skin to localize application and inhibit removal. For topical administration to internal tissue surfaces, the morphogen may be dispersed in a liquid tissue adhesive or other substance known to enhance adsorption to a tissue surface. For example, hydroxypropylcellulose or fibrinogen/thrombin solutions may be used to advantage. Alternatively, tissue-coating solutions, such as pectin-containing formulations may be used.

Alternatively, the morphogens described herein may be administered orally. Oral administration of proteins as therapeutics generally is not practiced as most proteins are readily degraded by digestive enzymes and acids in the mammalian digestive system before they can be absorbed into the bloodstream. However, the morphogens described herein typically are acid stable and protease-resistant (see, for example, U.S. Pat.No. 4,968,590.) In addition, at least one morphogen, OP-1, has been identified in mammary gland extract, colostrum and 57-day milk. Moreover, the OP-1 purified from mammary gland extract is morphogenically active. Specifically, this protein induces endochondral bone formation in mammals when implanted subcutaneously in

association with a suitable matrix material, using a standard in vivo bone assay, such as is disclosed in U.S. Pat.No. 4,968,590. Moreover, the morphogen also is detected in the bloodstream. Finally, soluble form morphogen, e.g., mature morphogen associated with the pro domain, is morphogenically active. These findings indicate that oral and parenteral administration are viable means for administering morphogens to an individual. In addition, while the mature forms of certain morphogens described herein typically are sparingly soluble, the morphogen form found in milk (and mammary gland extract and colostrum) is readily soluble, probably by association of the mature, morphogenically active form with part or all of the pro domain of the intact sequence and/or by association with one or more milk components. Accordingly, the compounds provided herein also may be associated with molecules capable of enhancing their solubility in vitro or in vivo.

The compounds provided herein also may be associated with molecules capable of targeting the morphogen or morphogen-stimulating agent to the desired tissue. For example, an antibody, antibody fragment, or other binding protein that interacts specifically with a surface molecule on cells of the desired tissue, may be used. Useful targeting molecules may be designed, for example, using the single chain binding site technology disclosed, for example, in U.S. Pat. No. 5,091,513.

As described above, the morphogens provided herein share significant sequence homology in the C-terminal active domains. By contrast, the sequences typically diverge significantly in the sequences which define the

pro domain. Accordingly, the pro domain is thought to be morphogen-specific. As described above, it is also known that the various morphogens identified to date are differentially expressed in the different tissues.

5 Accordingly, without being limited to any given theory, it is likely that, under natural conditions in the body, selected morphogens typically act on a given tissue. Accordingly, part or all of the pro domains which have been identified associated with the active
10 form of the morphogen in solution, may serve as targeting molecules for the morphogens described herein. For example, the pro domains may interact specifically with one or more molecules at the target tissue to direct the morphogen associated with the pro
15 domain to that tissue. Accordingly, another useful targeting molecule for targeting morphogen to a tissue of interest is part or all of a morphogen pro domain. For example, part or all of the pro domain of GDF-1, may be used to target a morphogen to nerve tissue.
20 Alternatively, part or all of the pro domains of OP-1 or CBMP2 may be used to target a morphogen to bone tissue, both of which proteins are found naturally associated with bone tissue.

25 The morphogens described herein are useful for providing neuroprotective effects to alleviate neural pathway damage associated with the body's immune/inflammatory response to an initial injury to nerve tissue. As used herein, a "neural pathway"
30 describes a nerve circuit for the passage of electric signals from a source to a target cell site and includes both the central nervous system (CNS) and peripheral nervous system (PNS). The pathway includes the neurons through which the electric impulse is
35 transported, including groups of interconnecting

neurons, the nerve fibers formed by bundled neuronal axons, and the glial cells surrounding and associated with the neurons. An inflammatory response to nerve tissue injury may follow trauma to nerve tissue, caused, for example, by an autoimmune (including autoantibody) dysfunction, neoplastic lesion, infection, chemical or mechanical trauma, or other disease. An exemplary nerve-related inflammatory disease is multiple sclerosis. Neural pathway damage also can result from a reduction or interruption, e.g., occlusion, of a neural blood supply, as in an embolic stroke, (e.g, ischemia or hypoxia-induced injury), or by other trauma to the nerve or surrounding material. In addition, at least part of the damage associated with a number of primary brain tumors also appears to be immunologically related. Application of the morphogen directly to the cells to be treated, or providing the morphogen to the mammal systemically, for example, intravenously or indirectly by oral administration, may be used to alleviate and/or inhibit the immunologically related response to a neural injury. Alternatively, administration of an agent capable of stimulating morphogen expression and/or secretion in vivo, preferably at the site of injury, also may be used. Where the injury is to be induced, as during surgery or other aggressive clinical treatment, the morphogen or agent may be provided prior to induction of the injury to provide a neuroprotective effect to the nerve tissue at risk.

30

Where the morphogen is intended for use as a therapeutic to alleviate tissue damage associated with an immune/inflammatory condition of the central nervous system (CNS) an additional problem must be addressed: overcoming the so-called "blood-brain barrier", the

35

brain capillary wall structure that effectively screens out all but selected categories of molecules present in the blood, preventing their passage into the brain.

The blood-brain barrier may be bypassed effectively by

5 direct infusion of the morphogen or morphogen-

stimulating agent into the brain. Alternatively, the

morphogen or morphogen-stimulating agent may be

modified to enhance its transport across the

blood-brain barrier. For example, truncated forms of

10 the morphogen or a morphogen-stimulating agent may be

most successful. Alternatively, the morphogen or

morphogen-stimulating agent may be modified to render

it more lipophilic, or it may be conjugated to another

molecule which is naturally transported across the

15 barrier, using standard means known to those skilled in

the art, as, for example, described in Pardridge,

Endocrine Reviews: 7:314-330 (1986) and U.S. Pat.

No. 4,801,575. A more detailed description of

morphogens for use in treating inflammatory conditions

20 in nerve tissue, including a model for evaluating

morphogen transport across the blood brain barrier is

disclosed in USSN 922,813, the disclosure of which is

incorporated herein by reference.

25 Finally, the morphogens or morphogen-stimulating

agents provided herein may be administered alone or in

combination with other molecules known to be beneficial

in the treatment compositions and methods described

herein, including, but not limited to anticoagulants,

30 free oxygen radical inhibiting agents, salicylic acid,

vitamin D, and other antiinflammatory agents. Psoriasis

treatments also may include ultra-violet light

treatment, zinc oxide and retinoids.

The compounds provided herein can be formulated into pharmaceutical compositions by admixture with pharmaceutically acceptable nontoxic excipients and carriers. As noted above, such compositions may be prepared for parenteral administration, particularly in the form of liquid solutions or suspensions; for oral administration, particularly in the form of tablets or capsules; or intranasally, particularly in the form of powders, nasal drops, or aerosols.

The compositions can be formulated for parenteral or oral administration to humans or other mammals in therapeutically effective amounts, e.g., amounts which provide appropriate concentrations for a time sufficient to alleviate the tissue destructive effects associated with the inflammatory response, including protecting tissue in anticipation of tissue damage.

As will be appreciated by those skilled in the art, the concentration of the compounds described in a therapeutic composition will vary depending upon a number of factors, including the dosage of the drug to be administered, the chemical characteristics (e.g., hydrophobicity) of the compounds employed, and the route of administration. The preferred dosage of drug to be administered also is likely to depend on such variables as the type and extent of progression of the tissue damage, the overall health status of the particular patient, the relative biological efficacy of the compound selected, the formulation of the compound excipients, and its route of administration. In general terms, the compounds of this invention may be provided in an aqueous physiological buffer solution containing about 0.001% to 10% w/v compound for parenteral administration. Typical dose ranges are

from about 10 ng/kg to about 1 g/kg of body weight per day; a preferred dose range is from about 0.1 μ g/kg to 100 mg/kg of body weight per day. Optimally, the morphogen dosage given in most cases is between 0.1-
5 100 μ g of protein per kilogram weight of the patient. No obvious morphogen induced pathological lesions are induced when mature morphogen (e.g., OP-1, 20 μ g) is administered daily to normal growing rats for 21 consecutive days. Moreover, 10 μ g systemic
10 injections of morphogen (e.g., OP-1) injected daily for 10 days into normal newborn mice does not produce any gross abnormalities.

15 In administering morphogens systemically in the methods of the present invention, preferably a large volume loading dose is used at the start of the treatment. The treatment then is continued with a maintenance dose. Further administration then can be determined by monitoring at intervals the levels of the
20 morphogen in the blood.

Where tissue injury is induced deliberately as part of, for example, a surgical procedure, the morphogen preferably is provided just prior to, or concomitant
25 with induction of the trauma. Preferably, the morphogen is administered prophylactically in a surgical setting.

Alternatively, an effective amount of an agent capable of stimulating endogenous morphogen levels may be administered by any of the routes described above.
30 For example, an agent capable of stimulating morphogen production and/or secretion from cells of affected tissue or a transplanted organ may be provided to a mammal, e.g., by direct administration of the morphogen to the tissue or organ. A method for identifying and

testing agents capable of modulating the levels of endogenous morphogens in a given tissue is described generally herein in Example 15, and in detail in copending USSN 752,859, filed August 30, 1991, the disclosure of which is incorporated herein by reference. Briefly, candidate compounds can be identified and tested by incubating the compound in vitro with a test tissue or cells thereof, for a time sufficient to allow the compound to affect the production, i.e., the expression and/or secretion, of a morphogen produced by the cells of that tissue.

For purposes of the present invention, the above-described morphogens effective in alleviating ischemic-reperfusion injury (or the agents that stimulate them, referred to herein collectively as "therapeutic agent") are administered prior to or during the restoration of oxygen (e.g., restoration of blood flow, reperfusion.) Where treatment is to follow an existing injury, the therapeutic agent preferably is administered as an intravenous infusion provided acutely after the hypoxic or ischemic condition occurs. For example, the therapeutic agent can be administered by intravenous infusion immediately after a cerebral infarction, a myocardial infarction, asphyxia, or a cardiopulmonary arrest. Where ischemia or hypoxia is deliberately induced as part of, for example, a surgical procedure where circulation to an organ or organ system is deliberately and/or transiently interrupted, e.g., in carotid enterectomy, coronary artery bypass, grafting, organ transplanting, fibrinolytic therapy, etc., the therapeutic agent preferably is provided just prior to, or concomitant with, reduction of oxygen to the tissue. Preferably, the therapeutic agent is administered prophylactically in a surgical setting.

Similarly, where hyperoxia induced-injury already has occurred, the morphogen is administered upon diagnosis. Where hyperoxia may be induced as, for example, during treatment of prematurely newborn babies, or patients suffering from pulmonary diseases such as emphysema, the therapeutic agent preferably is administered prior to administration of oxygen (e.g., prophylactically).

III. Examples

Example 1. Identification of Morphogen-Expressing Tissue

Determining the tissue distribution of morphogens may be used to identify different morphogens expressed in a given tissue, as well as to identify new, related morphogens. Tissue distribution also may be used to identify useful morphogen-producing tissue for use in screening and identifying candidate morphogen-stimulating agents. The morphogens (or their mRNA transcripts) readily are identified in different tissues using standard methodologies and minor modifications thereof in tissues where expression may be low. For example, protein distribution may be determined using standard Western blot analysis or immunofluorescent techniques, and antibodies specific to the morphogen or morphogens of interest. Similarly, the distribution of morphogen transcripts may be determined using standard Northern hybridization protocols and transcript-specific probes.

Any probe capable of hybridizing specifically to a transcript, and distinguishing the transcript of

interest from other, related transcripts may be used. Because the morphogens described herein share such high sequence homology in their active, C-terminal domains, the tissue distribution of a specific morphogen transcript may best be determined using a probe specific for the pro region of the immature protein and/or the N-terminal region of the mature protein. Another useful sequence is the 3' non-coding region flanking and immediately following the stop codon.

10 These portions of the sequence vary substantially among the morphogens of this invention, and accordingly, are specific for each protein. For example, a particularly useful Vgr-1-specific probe sequence is the PvuII-SacI fragment, a 265 bp fragment encoding both a portion of the untranslated pro region and the N-terminus of the mature sequence (see Lyons et al. (1989) PNAS 86:4554-4558 for a description of the cDNA sequence).

15 Similarly, particularly useful mOP-1-specific probe sequences are the BstXI-BglI fragment, a 0.68 Kb sequence that covers approximately two-thirds of the mOP-1 pro region; a StuI-StuI fragment, a 0.2 Kb sequence immediately upstream of the 7-cysteine domain; and the EarI-PstI fragment, an 0.3 Kb fragment containing a portion of the 3'untranslated sequence (See Seq. ID No. 18, where the pro region is defined essentially by residues 30-291.) Similar approaches may be used, for example, with hOP-1 (Seq. ID No. 16) or human or mouse OP-2 (Seq. ID Nos. 20 and 22.)

30 Using these morphogen-specific probes, which may be synthetically engineered or obtained from cloned sequences, morphogen transcripts can be identified in mammalian tissue, using standard methodologies well known to those having ordinary skill in the art.

35 Briefly, total RNA is prepared from various adult

murine tissues (e.g., liver, kidney, testis, heart, brain, thymus and stomach) by a standard methodology such as by the method of Chomczyaski et al. ((1987) Anal. Biochem 162:156-159) and described below. Poly (A)+ RNA is prepared by using oligo (dT)-cellulose chromatography (e.g., Type 7, from Pharmacia LKB Biotechnology, Inc.). Poly (A)+ RNA (generally 15 µg) from each tissue is fractionated on a 1% agarose/formaldehyde gel and transferred onto a Nytran membrane (Schleicher & Schuell). Following the transfer, the membrane is baked at 80°C and the RNA is cross-linked under UV light (generally 30 seconds at 1 mW/cm²). Prior to hybridization, the appropriate probe is denatured by heating. The hybridization is carried out in a lucite cylinder rotating in a roller bottle apparatus at approximately 1 rev/min for approximately 15 hours at 37°C using a hybridization mix of 40% formamide, 5 x Denhardts, 5 x SSPE, and 0.1% SDS. Following hybridization, the non-specific counts are washed off the filters in 0.1 x SSPE, 0.1% SDS at 50°C.

Examples demonstrating the tissue distribution of various morphogens, including Vgr-1, OP-1, BMP2, BMP3, BMP4, BMP5, GDF-1, and OP-2 in developing and adult tissue are disclosed in co-pending USSN 752,764, and in Ozkaynak, et al., (1991) Biochem. Biophys. Res. Commn. 179:116-123, and Ozkaynak, et al. (1992) (JBC, in press), the disclosures of which are incorporated herein by reference. Using the general probing methodology described herein, northern blot hybridizations using probes specific for these morphogens to probe brain, spleen, lung, heart, liver and kidney tissue indicate that kidney-related tissue appears to be the primary expression source for OP-1, with brain, heart and lung tissues being secondary

sources. OP-1 RNA also was identified in salivary glands, specifically rat parotid glands, using this probing methodology. Lung tissue appears to be the primary tissue expression source for Vgr-1, BMP5, BMP4 and BMP3. Lower levels of Vgr-1 also are seen in kidney and heart tissue, while the liver appears to be a secondary expression source for BMP5, and the spleen appears to be a secondary expression source for BMP4. GDF-1 appears to be expressed primarily in brain tissue. To date, OP-2 appears to be expressed primarily in early embryonic tissue. Specifically, northern blots of murine embryos and 6-day post-natal animals shows abundant OP2 expression in 8-day embryos. Expression is reduced significantly in 17-day embryos and is not detected in post-natal animals.

Example 2. Active Morphogens in Body Fluids

OP-1 expression has been identified in saliva (specifically, the rat parotid gland, see Example 1), human blood serum, and various milk forms, including mammary gland extract, colostrum, and 57-day bovine milk. Moreover, and as described in USSN 923,780, the disclosure of which is incorporated herein by reference, the body fluid-extracted protein is morphogenically active. The discovery that the morphogen naturally is present in milk and saliva, together with the known observation that mature, active OP-1 is acid-stable and protease-resistant, indicate that oral administration is a useful route for therapeutic administration of morphogen to a mammal. Oral administration typically is the preferred mode of delivery for extended or prophylactic therapies. In addition, the identification of morphogen in all milk forms, including colostrum, suggests that the protein

may play a significant role in tissue development,
including skeletal development, of juveniles.

2.1 Morphogen Detection in Milk

OP-1 was partially purified from rat mammary gland
extract and bovine colostrum and 57 day milk by passing
these fluids over a series of chromatography columns:
(e.g., cation-exchange, affinity and reverse phase). At
each step the eluant was collected in fractions and
these were tested for the presence of OP-1 by standard
immunoblot. Immunoreactive fractions then were
combined and purified further. The final, partially
purified product then was examined for the presence of
OP-1 by Western blot analysis using OP-1-specific
antisera, and tested for in vivo and in vitro activity.

OP-1 purified from the different milk sources were
characterized by Western blotting using antibodies
raised against OP-1 and BMP2. Antibodies were prepared
using standard immunology protocols well known in the
art, and as described generally in Example 15, below,
using full-length E. coli-produced OP-1 and BMP2 as the
immunogens. In all cases, the purified OP-1 reacted
only with the anti-OP-1 antibody, and not with
anti-BMP2 antibody.

The morphogenic activity of OP-1 purified from
mammary gland extract was evaluated in vivo essentially
following the rat model assay described in U.S. Pat.
No. 4,968,590, hereby incorporated by reference.
Briefly, a sample was prepared from each OP-1
immunoreactive fraction of the mammary gland
extract-derived OP-1 final product by lyophilizing a
portion (33%) of the fraction and resuspending the

protein in 220 μ l of 50% acetonitrile/0.1% TFA. After vortexing, 25 mg of collagen matrix was added. The samples were lyophilized overnight, and implanted in Long Evans rats (Charles River Laboratories, Wilmington, MA, 28-35 days old). Each fraction was implanted in duplicate. For details of the collagen matrix implantation procedure, see, for example, U.S. Pat. No. 4,968,590, hereby incorporated by reference. After 12 days, the implants were removed and evaluated for new bone formation by histological observation as described in U.S. Patent No. 4,968,590. In all cases, the immunoreactive fractions were osteogenically active.

2.2 Morphogen Detection in Serum

Morphogen may be detected in serum using morphogen-specific antibodies. The assay may be performed using any standard immunoassay, such as Western blot (immunoblot) and the like. Preferably, the assay is performed using an affinity column to which the morphogen-specific antibody is bound and through which the sample serum then is poured, to selectively extract the morphogen of interest. The morphogen then is eluted. A suitable elution buffer may be determined empirically by determining appropriate binding and elution conditions first with a control (e.g., purified, recombinantly-produced morphogen.) Fractions then are tested for the presence of the morphogen by standard immunoblot, and the results confirmed by N-terminal sequencing. Preferably, the affinity column is prepared using monoclonal antibodies. Morphogen concentrations in serum or other fluid samples then may be determined using standard protein quantification

techniques, including by spectrophotometric absorbance or by quantitation of conjugated antibody.

Presented below is a sample protocol for

5 identifying OP-1 in serum. Following this general methodology other morphogens may be detected in body fluids, including serum. The identification of morphogen in serum further indicates that systemic administration is a suitable means for providing
10 therapeutic concentrations of a morphogen to an individual, and that morphogens likely behave systemically as endocrine-like factors. Finally, using this protocol, fluctuations in endogenous morphogen levels can be detected, and these altered levels may be
15 used as an indicator of tissue dysfunction. Alternatively, fluctuations in morphogen levels may be assessed by monitoring morphogen transcription levels, either by standard northern blot analysis as described in Example 1, or by in situ hybridization, using a
20 labelled probe capable of hybridizing specifically to morphogen "mRNA", and standard RNA hybridization protocols well described in the art and described generally in Example 1.

25 OP-1 was detected in human serum using the following assay. A monoclonal antibody raised against mammalian, recombinantly produced OP-1 using standard immunology techniques well described in the art and described generally in Example 15, was immobilized by
30 passing the antibody over an agarose-activated gel (e.g., Affi-GelTM, from Bio-Rad Laboratories, Richmond, CA, prepared following manufacturer's instructions) and used to purify OP-1 from serum. Human serum then was passed over the column and eluted with 3M
35 K-thiocyanate. K-thiocyanate fractions then were

dialyzed in 6M urea, 20mM PO₄, pH 7.0, applied to a C8 HPLC column, and eluted with a 20 minute, 25-50% acetonitrile/0.1% TFA gradient. Mature, recombinantly produced OP-1 homodimers elute between 20-22 minutes.

- 5 Fractions then were collected and tested for the presence of OP-1 by standard immunoblot using an OP-1 specific antibody as for Example 2.A.

10 Administered or endogenous morphogen levels may be monitored in the therapies described herein by comparing the quantity of morphogen present in a body fluid sample with a predetermined reference value, for example, to evaluate the efficiency of a therapeutic protocol, and the like. In addition, fluctuations in the level of endogenous morphogen antibodies may be detected by this method, most likely in serum, using an antibody or other binding protein capable of interacting specifically with the endogenous morphogen antibody. Detected fluctuations in the levels of the morphogen or endogenous antibody may be used, for example, as indicators of a change in tissue status. For example, as damaged tissue is regenerated and the tissue or organ's function returns to "normal" and, in the absence of additional tissue damage, lower doses of morphogen may be required, and a higher level of circulating morphogen antibody may be measured.

Example 3. Effect of Morphogen after the Onset of the Ischemic Process

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The cardioprotective effect of morphogens following ischemic-reperfusion injury in a mammal can readily be assessed in a rat model. In this example, morphogen (e.g., OP-1) is administered just prior to the onset of the ischemic process in experimentally-induced

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reference. Briefly, loss of myocardial tissue function following ischemia and reperfusion is assayed by measuring loss of myocardial creatine kinase activity (CK) and loss of endothelium-dependent vasorelaxation function (see Example 4, below).

In a first group of ether-anesthetized rats, the left coronary artery was occluded just proximal to the first main branch with a silk ligature to induce a myocardial infarction (MI). The ligature was removed 10 minutes after occlusion to allow for coronary reperfusion. This first group is referred to herein as the "myocardial infarcted" (MI) group. A second group of rats underwent the same procedure except that the coronary artery was not occluded, and thus no myocardial infarction occurred. The second group of rats is referred to herein as the "sham myocardial infarcted group" (SHAM MI).

The first group of rats, the MI group of rats, further was divided into three sub-groups. 2µg of morphogen (OP-1) were injected intravenously into the first sub-group of MI rats 10 minutes after ligation, immediately before reperfusion; into the second sub-group of MI rats 20 µg of OP-1 were injected intravenously 10 minutes after ligation and immediately before reperfusion; and into the third sub-group of MI rats (control) was injected vehicle only, e.g., 0.9% NaCl, as for the OP-1 treated rats.

Twenty-four hours later, the hearts were removed from all of the rats and the levels of creatine kinase (CK) from the left ventricle (the infarcted region) and from the interventricular septum (the control nonischemic region) were determined by standard means. By comparing the difference in CK activities in both regions, the amount of CK activity lost from the infarcted region was used as an index of cardiac cellular injury to the infarcted region.

As shown in Figure 1, the data indicate that morphogens (e.g., OP-1) can provide significant cardioprotective effect when provided to ischemic tissue. In the figure, CK loss is graphed as the difference in specific CK activity between the interventricular septum and the left ventricle.

The loss of CK activity by the subgroup of MI rats which received 2 μ g of OP-1 just before reperfusion showed some protection as compared with the control MI rats which received injections of vehicle alone, when the levels from both subgroups are measured against, and compared to, the levels obtained for the SHAM MI control. Significant cardioprotection was observed in the subgroup of MI rats which received 20 μ g of OP-1 immediately before reperfusion as compared with the control MI rats which received injections of vehicle alone, when the levels from both subgroups are measured against, and compared to, the levels contained within the SHAM MI control.

These data indicate that OP-1 offers significant cardiac protection when administered after ischemia and before reperfusion.

A variation of this example also may be performed providing morphogen to the animal prior to induction of ischemia. The experiments may be performed both in normal and immune-compromised rats to assess the cardioprotective effects of morphogen administered prior to ischemia.

Example 4. Vasodilation of Myocardial Infarcted Cardiac Tissue Treated with Morphogen

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Certain vasodilators like acetylcholine (ACh) and adenosine diphosphate (ADP, an immune mediator) exert their vasodilation activity only in the presence of intact endothelium, which is stimulated to release a substance termed endothelium-derived relaxing factor (EDRF). If the endothelium is injured so that EDRF is not released, no vasodilation occurs in response to these endothelium-dependent agents. In contrast, several other vasodilators including nitroglycerine (NTG) and nitroprusside, are endothelium-independent dilators, as they dilate blood vessels directly.

The present example demonstrates the ability of OP-1 to prevent the loss of cardioendothelium-dependent relaxation (EDR) activity in the coronary microvasculature following reperfusion of ischemic myocardium, and their ability to reduce myocardial injury 24 hours after morphogen treatment. Briefly, 2 or 24 hours after morphogen treatment ischemia-reperfusion injury is induced in isolated rat hearts, the reperfused hearts are vasodilated with either ACh or NTG. In the absence of morphogen treatment, injured tissue should inhibit ACh-induced vasodilation, but not NTG-induced vasodilation. Morphogen treatment

in expected to enhance ACh-induced vasodilation in the
reperfused hearts.

Accordingly, 48 adult male Sprague-Dawley rats
5 (250-330 g) were divided into eight groups of 6 rats
each. Twelve rats were subjected to sham myocardial
infarcts (SHAM MI) as described in Example 3. The
hearts of the remaining 36 rats were isolated as
follows: one set of twelve rats was injected
10 intravenously with OP-1 24 hours prior to isolation of
the heart; another set of rats was injected
intravenously with 20 μ g of OP-1 2 hours prior to
isolation of the heart; the final group of rats was
injected with vehicle only (e.g., 0.9% NaCl.). The rats
15 then were anesthetized with pentobarbital sodium
(35 mg/kg, intraperitoneal); their hearts were isolated
and perfused by the Langendorff method at a constant
flow (15 ml/min) with oxygenated Krebs-Henseleit
solution (Aoki et al. (1988) J. Pharmacol. 95:35).
20 Each group of rats then were divided into two
subgroups of six rats each. Twenty minutes before
reperfusion, coronary vasodilator response was measured
by inducing constriction with 0.05 μ mol U-44619 (9,11-
methanoepoxyprostaglandin H₂) followed by a
25 vasodilating agent 3 minutes later: subgroup one -
15 nmol ACh; subgroup 2 - 15 nmol NTG and the increase
in coronary perfusion pressure (CPP) level measured as
an indication of vasodilation. When CPP levels
returned to normal, the hearts were subjected to
30 ischemia by reducing coronary infusion to 15% of
control flow for 30 minutes, then reestablishing normal
flow, i.e., reperfusion, for an additional 20 minutes.

The vasodilator response then was remeasured by
35 constriction and administration of vasodilating agent

as described above.

The results of these experiments are shown in FIG 2. Before the ischemic event, both Ach and NTG gave normal vasorelaxant results in all events. The hearts which received OP-1 24 hours prior to ischemia showed an approximately 70% response to ACh while the hearts which received OP-1 2 hours prior to ischemia showed a 55% response to ACh. The group which received vehicle alone showed a 40% response to ACh. Finally, the control group which was not subjected to ischemia showed an ACh response of approximately 95%. This shows that endothelium-dependent vasodilators exert a reduced vasodilator response following ischemia and reperfusion in the rat heart. Moreover, OP-1 significantly preserved endothelium-dependent dilation when provided 24 hours prior to induction of myocardial ischemia. No defect in vasodilation occurred in response to the direct vasodilator (NTG); NTG-induced vasodilation activities were 95% of initial in hearts subject to ischemia and 100% of initial nonischemic hearts.

Example 5. Effect of Morphogen on Neutrophil Adherence

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The role of neutrophil adherence in endothelium dysfunction and the cardioprotective effects of morphogens in modulating this activity can be assessed using a standard polymorphonuclear neutrophil (PMN) adherence assay such as described in Lefer et al., (1992) J. Mol. Cell. Cardiol. 24: 385-393, disclosed hereinabove by reference. Briefly, segments of superior mesenteric artery were isolated from rats which had either been treated with morphogen (OP-1, 20 μ g) or 0.9% NaCl, 24 h prior to isolation of the

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artery. The segments were cleaned, cut into transverse rings of 1-2mm in length, and these were subsequently cut open and incubated in K-H solution at 37°C, pH 7.4. Neutrophils were prepared and fluorescently labelled using standard procedures (e.g., leukocytes were isolated from rats essentially following the procedure of Pertroft et. al. (1968) Exp Cell Res 50: 355-368, washed in phosphate buffered saline (PBS), purified by gradient centrifugation; and labelled by the method of Yuan et. al. (1990) Microvasc Res 40: 218-229.

Labelled neutrophils then were added to open ring baths and activated with 100nM leukotriene B₄ (LTB₄). Rings were incubated for 20 minutes and the number of neutrophils adhering to the endothelial surface then determined visually by fluorescent microscopy.

As shown in Figure 3, unstimulated PMNs (i.e., PMNs alone) added to the baths did not significantly adhere to the vascular endothelium. In rings taken from rats injected with 0.9% NaCl, activation of neutrophils with LTB₄ (100 nM) greatly increased the number of PMNs adherent to the endothelium (P<0.001). OP-1 (20 µg administered 24 h prior) significantly inhibited adherence of PMNs activated by LTB₄ (P<0.01 from control).

Example 6. In Vivo Models for Ischemic-Reperfusion Protection in Lung, Nerve and Renal Tissue.

Other tissues seriously affected by ischemic-reperfusion injury include neural tissue, renal tissue and lung tissue. The effect of morphogens on alleviating the ischemic-reperfusion injury in these

tissues may be assessed using methodologies and models known to those skilled in the art, and disclosed below. Similarly, a methodology also is provided for assessing the tissue-protective effects of a morphogen on damaged lung tissue following hyperoxia injury.

For example, the rabbit embolic stroke model provides a useful method for assessing the effect of morphogens on tissue injury following cerebral ischemia-reperfusion. The protocol disclosed below is essentially that of Phillips et al. (1989) Annals of Neurology 25:281-285, the disclosure of which is herein incorporated by reference. Briefly, white New England rabbits (2-3kg) are anesthetized and placed on a respirator. The intracranial circulation then is selectively catheterized by the Seldinger technique. Baseline cerebral angiography then is performed, employing a digital substration unit. The distal internal carotid artery or its branches then is selectively embolized with 0.035 ml of 18-hour-aged autologous thrombus. Arterial occlusion is documented by repeat angiography immediately after embolization. After a time sufficient to induce cerebral infarcts (15 minutes or 90 minutes), reperfusion is induced by administering a bolus of a reperfusion agent such as the TPA analogue Fb-FB-CF (e.g., 0.8 mg/kg over 2 minutes).

The effect of morphogen on cerebral infarcts can be assessed by administering varying concentrations of morphogens, e.g., OP1, at different times preceding or following embolization and/or reperfusion. The rabbits are sacrificed 3-14 days post embolization and their brains prepared for neuropathological examination by fixing by immersion in 10% neutral buffered formalin

for at least 2 weeks. The brains then are sectioned in a coronal plane at 2-3 mm intervals, numbered and submitted for standard histological processing in paraffin, and the degree of neutral tissue necrosis determined visually.

The renal-protective effects of morphogens on renal ischemia-reperfusion injury readily can be assessed using the mouse model disclosed by Ouellette, et al. (1990), J. Clin. Invest. 85:766-771, the disclosure of which is hereby incorporated by reference. Briefly, renal ischemia is induced surgically in 35-45 days old out-bred Swiss male mice by performing a standard right nephrectomy, and occluding the artery to the left kidney with a microaneurism clamp for 10-30 minutes. Morphogen then may be provided parentally at various times prior to or following, occlusion and/or reperfusion. The effects of morphogen then may be assessed by biological and histological evaluation using standard techniques well known in the art.

The tissue protective effects of morphogen on tissue exposed to lethally high oxygen concentrations may be assessed by the following procedure. Adult rats (275-300 gms) first are provided with morphogen (e.g., hOP1) or vehicle only, and then are exposed to 96-98% oxygen essentially as described by Rinaldo et al (1983) Am. Rev. Respir. Dis. 130:1065, to induce hyperoxia. Animals are housed in plastic cages (38 cm x 48 cm x 21 cm). A cage containing 4-5 animals is placed in a 75 liter water-sealed plexiglass chamber. An atmosphere of 96-98% oxygen then is maintained by delivery of O₂ gas (liquid O₂). Gas flow through the chamber is adjusted to maintain at least 10 air changes/hr., temperature at 22 ± 1°C, minimal levels of condensation

within the cage, and carbon dioxide concentration of < 0.5% as measured with a mass spectrophotometric medical gas analyzer.

5 At the end of 72 hours all survivors are observed at room air for 1.5 hours and at longer time periods to assess degree of respiratory distress and cyanosis induced by the initial insult and subsequent immune insult and subsequent immune cell-mediated damage.

10 The number of survivors at the end of the challenge is recorded and the treated groups compared with the untreated control group by chi-square test of proportions. Several of the surviving animals for each group are randomly chosen for histological processing
15 of lung tissue.

Lung tissue for histological processing is fixed by infusion of 10% buffered formalin through a tracheal cannula at a constant pressure of 20 cm H₂O. After
20 fixation for 24-48 hours, sections from each lobe are cut and subsequently stained with hematoxylin and eosin. Coded slides then are examined, preferably in a double-blind fashion for evidence of pathological changes such as edema, interstitial cellularity, and
25 inflammatory response.

Example 7. Morphogen Inhibition of Cellular and Humoral Inflammatory Response

30 Morphogens described herein inhibit multinucleation of mononuclear phagocytic cells under conditions where these cells normally would be activated, e.g., in response to a tissue injury or the presence of a foreign substance. For example, in the absence of
35 morphogen, an implanted substrate material (e.g.,

implanted subcutaneously) composed of, for example, mineralized bone, a ceramic such as titanium oxide or any other substrate that provokes multinucleated giant cell formation, rapidly becomes surrounded by

5 multinucleated giant cells, e.g., activated phagocytes stimulated to respond and destroy the foreign object.

In the presence of morphogen however, the recruited cells remain in their mononuclear precursor form and the matrix material is undisturbed. Figure 4

10 illustrates this effect of morphogens, in a schematic representation of histology results of a titanium oxide substrate implanted subcutaneously. In the figure, "mg" means mononuclear giant cells and "ob" means osteoblasts. The substrate represented in Fig. 4B was
15 implanted together with morphogen (OP-1) and newly formed osteoblasts are evident surrounding the substrate. By contrast, the substrate represented in Fig. 4A was implanted without morphogen and extensive multinucleated giant cell formation is evident
20 surrounding the substrate. Accordingly, the morphogens' effect in inhibiting excessive bone mass loss in a mammal also may include inhibiting activation of these cells.

25 In addition, the morphogens described herein also suppress antibody production stimulated in response to a foreign antigen in a mammal. Specifically, when bovine bone collagen matrix alone was implanted in a bony site in a rat, a standard antibody response to the
30 collagen is stimulated in the rat as determined by standard anti-bovine collagen ELISA experiments performed on blood samples taken at four week intervals following implantation (e.g., between 12 and 20 weeks.) Serum anti-collagen antibody titers, measured by ELISA
35 essentially following the procedure described by

Nagler-Anderson et al, (1986) PNAS 83:7443-7446, the disclosure of which is incorporated herein by reference, increased consistently throughout the experiment. However, when the matrix was implanted together with a morphogen (e.g., OP-1, dispersed in the matrix and adsorbed thereto, essentially as described in U.S. Pat. No. 4,968,590) anti-bovine collagen antibody production was suppressed significantly. This ability of morphogen to suppress the humoral response is further evidence of morphogen utility in alleviating tissue damage associated with autoimmune diseases, including autoantibody diseases, such as rheumatoid arthritis.

15 Example 8. Morphogen protection of Gastrointestinal Tract Mucosa from Ulceration and Inflammation

Oral mucositis is a gastrointestinal tract inflammatory disease which involves ulcerations of the mouth mucosa as a consequence of, e.g., radiation therapy or chemotherapy. While not typically a chronic disease, the tissue destructive effects of oral mucositis mirror those of chronic inflammatory diseases such as IBD. The example below demonstrates morphogen efficacy in protecting the oral mucosa from oral mucositis in a hamster model, including both inhibiting inflammatory ulceration and enhancing regeneration of ulcerated tissue. Details of the protocol can be found in Sonis, et al., (1990) Oral Surg. Oral Med. Oral Pathol 69: 437-443, the disclosure of which is incorporated herein by reference. Based on these data, the morphogens described herein should be efficacious in treating chronic inflammatory diseases including

IBD, arthritis, psoriasis and psoriatic arthritis, multiple sclerosis, and the like.

Golden syrian hamsters (6-8 wks old, Charles River Laboratories, Wilmington, MA) were divided into 3 test groups: Group 1, a placebo (e.g., saline) control, and a morphogen low dose group (100 ng) and a morphogen high dose group (1 μ g), Groups 2 and 3, respectively. Morphogen dosages were provided in 30% ethanol. Each group contained 12 animals.

Beginning on day 0 and continuing through day 5, Groups 2 and 3 received twice daily morphogen applications. On day 3, all groups began the mucositis-induction procedure. 5-fluorouracil (60 mg/kg) was injected intraperitoneally on days 3 and 5. On day 7, the right buccal pouch mucosa was superficially irritated with a calibrated 18 gauge needle. In untreated animals, severe ulcerative mucositis was induced in at least 80% of the animals by day 10.

For each administration of the vehicle control (placebo) or morphogen, administration was performed by first gently drying the cheek pouch mucosa, then providing an even application over the mucosal surface of the vehicle or morphogen material. A hydroxypropylcellulose-based coating was used to maintain contact of the morphogen with the mucosa. This coating provided at least 4 hours of contact time.

On day 12, two animals in each group were sacrificed for histological studies. The right buccal pouch mucosa and underlying connective tissue were dissected and fixed in 10% formalin using standard

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Example 9. Morphogen Effect on Fibrogenesis and Scar Tissue Formation

The morphogens described herein induce tissue

morphogenesis of damaged or lost tissue. The ability of these proteins to regenerate new tissue enhances the anti-inflammatory effect of these proteins. Provided below are a series of in vitro experiments demonstrating the ability of morphogens to induce migration and accumulation of mesenchymal cells. In addition, the experiments demonstrate that morphogens, unlike TGF- β , do not stimulate fibrogenesis or scar tissue formation. Specifically, morphogens do not stimulate production of collagen, hyaluronic acid (HA) or metalloproteinases in primary fibroblasts, all of which are required for fibrogenesis or scar tissue formation. By contrast, TGF- β , a known inducer of fibrosis, but not of tissue morphogenesis, does stimulate production of these fibrosis markers.

Chemotaxis and migration of mesenchymal progenitor cells were measured in modified Boyden chambers essentially as described by Fava, R.A. et al (1991) J. Exp. Med. 173: 1121-1132, the disclosure of which is incorporated herein by reference, using polycarbonate filters of 2, 3 and 8 micron pores to measure migration of progenitor neutrophils, monocytes and fibroblasts. Chemotaxis was measured over a range of morphogen concentrations, e.g., 10^{-20} M to 10^{-12} M OP-1. For progenitor neutrophils and monocytes, 10^{-18} - 10^{-17} M OP-1 consistently induced maximal migration, and 10^{-14} to 10^{-13} M OP-1 maximally induced migration of progenitor fibroblasts. In all cases the chemotactic activity could be inhibited with anti-OP-1 antibody. Similar

migration activities also were measured and observed with TGF- β .

The effect of morphogen on fibrogenesis was
5 determined by evaluating fibroblast production of hyaluronic acid (HA), collagen, collagenase and tissue inhibitor of metalloproteinases (TIMP).

Human fibroblasts were established from explants of
10 infant foreskins and maintained in monolayer culture using standard culturing procedures. (See, for example, (1976) J. Exp. Med. 144: 1188-1203.) Briefly, fibroblasts were grown in maintenance medium consisting of Eagle's MEM, supplemented with nonessential amino
15 acids, ascorbic acid (50 μ g/ml), NaHCO₃ and HEPES buffers (pH 7.2), penicillin (100 U/ml), streptomycin (100 μ g/ml), amphotericin B (1 μ g/ml) and 9% heat inactivated FCS. Fibroblasts used as target cells to measure chemotaxis were maintained in 150 mm diameter
20 glass petri dishes. Fibroblasts used in assays to measure synthesis of collagen, hyaluronic acid, collagenase and tissue inhibitors of metalloproteinases (TIMP) were grown in 100 mm diameter plastic tissue culture petri dishes.

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The effects of morphogen on fibroblast production of hyaluronic acid, collagens, collagenase and TIMP were determined by standard assays (See, for example, Posttethwaite et al. (1989) J. Clin. Invest. 83: 629-
30 636, Posttethwaithe (1988) J. Cell Biol. 106: 311-318 and Clark et al (1985) Arch. Bio-chem Biophys. 241: 36-44, the disclosures of which are incorporated by reference.) For these assays, fibroblasts were transferred to 24-well tissue culture plates at a
35 density of 8×10^4 cells per well. Fibroblasts were

grown confluency in maintenance medium containing 9% FCS for 72 h and then grown in serum-free maintenance medium for 24 h. Medium was then removed from each well and various concentrations of OP-1 (recombinantly produced mature or soluble form) or TGF- β -1 (R&D Systems, Minneapolis) in 50 μ l PBS were added to triplicate wells containing the confluent fibroblast monolayers. For experiments that measured production of collagenase and TIMP, maintenance medium (450 μ l) containing 5% FCS was added to each well, and culture supernatants were harvested from each well 48 h later and stored at -70°C until assayed. For experiments that assessed HA production, maintenance medium (450 μ l) containing 2.5% FCS was added to each well, and cultures grown for 48 h. For experiments that measured fibroblast production of collagens, serum-free maintenance medium (450 μ l) without non-essential amino acids was added to each well and cultures grown for 72 h. Fibroblast production of HA was measured by labeling newly synthesized glycosaminoglycans (GAG) with [3 H]-acetate the last 24 h of culture and quantitating released radioactivity after incubation with hyaluronidase from Streptomyces hyalurolyticus (ICN Biochemicals, Cleveland, OH) which specifically degrades hyaluronic acid. Production of total collagen by fibroblasts was measured using a collagenase-sensitive protein assay that reflects [3 H]-proline incorporation the last 24 h of culture into newly synthesized collagens. Collagenase and TIMP protein levels in fibroblast cultures supernatants was measured by specific ELISAs.

As shown in Fig. 6, OP1 does not stimulate significant collagen or HA production, as compared with TGF- β . In the figure, panel A shows OP-1 effect on

collagen production, panel B shows TGF- β effect on collagen production, and panels C and D show OP-1 (panel C) and TGF- β (panel D) effect on HA production. The morphogen results were the same whether the soluble or mature form of OP1 was used. By contrast, the latent form of TGF- β (e.g., pro domain-associated form of TGF- β) was not active.

Example 10. Morphogen Inhibition of Epithelial Cell Proliferation

This example demonstrates the ability of morphogens to inhibit epithelial cell proliferation in vitro, as determined by ^3H -thymidine uptake using culture cells from a mink lung epithelial cell line (ATCC No. CCL 64), and standard mammalian cell culturing procedures. Briefly, cells were grown to confluency in Eagle's minimum essential medium (EMEM) supplemented with 10% fetal bovine serum (FBS), 200 units/ml penicillin, and 200 $\mu\text{g}/\text{ml}$ streptomycin, and used to seed a 48-well cell culture plate at a cell density of 200,000 cells per well. When this culture became confluent, the media was replaced with 0.5 ml of EMEM containing 1% FBS and penicillin/streptomycin and the culture incubated for 24 hours at 37 C. Morphogen test samples in EMEM containing 5% FBS then were added to the wells, and the cells incubated for another 18 hours. After incubation, 1.0 μCi of ^3H -thymidine in 10 μl was added to each well, and the cells incubated for four hours at 37 C. The media then was removed and the cells washed once with ice-cold phosphate-buffer saline and DNA precipitated by adding 0.5 ml of 10% TCA to each well and incubating at room temperature of 15 minutes. The cells then were washed three times with ice-cold distilled water, lysed with 0.5 ml 0.4 M NaOH, and the

lysate from each well then transferred to a scintillation vial and the radioactivity recorded using a scintillation counter (Smith-Kline Beckman).

5 The results are presented in Table III, below. The anti-proliferative effect of the various morphogens tested was expressed as the counts of 3H-thymidine (x 1000) integrated into DNA, and were compared with untreated cells (negative control) and TGF- β (1 ng), a
10 local-acting factor also known to inhibit epithelial cell proliferation. COP-5 and COP-7 are biosynthetic constructs that previously have been shown to have osteogenic activity, capable of inducing the complete cascade resulting in endochondral bone formation in a
15 standard rat bone assay (see U.S. Pat. No. 5,011,691.) The morphogens significantly inhibit epithelial cell proliferation. Similar experiments, performed with the morphogens COP-16, bOP (bone-purified osteogenic protein, a dimeric protein comprising CBMP2 and OP-1),
20 and recombinant OP-1, also inhibit cell proliferation. bOP and COP-16 also induce endochondral bone formation (see US Pat. No. 4,968,590 and 5,011,691.)

TABLE III

25

	<u>Thymidine uptake (x 1000)</u>
control	50.048, 53.692
COP-7-1 (10 ng)	11.874
COP-7-2 (3 ng)	11.136
30 COP-5-1 (66 ng)	16.094
COP-5-2 (164 ng)	14.43
TGF- β (1 ng)	1.86, 1.478

Example 11. Morphogen Treatment of a Systemic
Inflammatory Disease

The following example provides a rat adjuvant-
5 induced arthritis model for demonstrating morphogen
efficacy in treating arthritis and other systemic
inflammatory diseases. Rat adjuvant-induced arthritis
induces a systemic inflammatory disease with bone and
cartilage changes similar to those observed in
10 rheumatoid arthritis, but in an accelerated time span
(see, for example, Pearson (1964) Arth. Rheum. 7:80).
A detailed description of the protocol is provided in
Walz, et al., (1971) J. Pharmac. Exp. Ther. 178: 223-
231, the disclosure of which is incorporated herein by
15 reference.

Briefly, Sprague-Dawley female rats (e.g., Charles
River Laboratories, Wilmington, MA) are randomized into
3 groups: control; morphogen, low dose (e.g., 1-
20 10 μ g/kg weight per day) and morphogen, high dose
(e.g., 10-20 μ g/kg weight per day), referred to as
Groups 1, 2, and 3, respectively.

Adjuvant arthritis is induced in all three groups
25 by injection of 0.05 ml of a suspension of 1.5% dead
Mycobacterium butyricum in mineral oil into the
subplantar surface of the right hand paw. On Day 18
after adjuvant injection, the limb volumes of both hind
limbs are determined. In the absence of morphogen
30 treatment, a systemic arthritic condition is induced in
the rats by this time, as determined by rats with
significant swelling of the uninjected hind limbs (<
2.3 ml, volume measured by mercury displacement).
Subsequent determinations of paw edema and x-ray scores
35 are made on the uninjected hind limb. Rats in Group 2

and 3 also are dosed orally daily, beginning on Day 1, with morphogen. Limb volumes are recorded on Days 29 and 50 after adjuvant injection and edema determined by volume difference compared to Day 18. The uninjected hind limb on each rat was x-rayed on Day 50 and the joint damage assayed on an arbitrary scale of 1 to 10 (1=no damage, 10=maximum damage). Data on differences between control and treated groups (Day 29 edema, Day 50 edema and Day 50 x-ray scores) are analyzed by using a standard "t-test". Morphogen-treated rats show consistently reduced joint damage (e.g., decreased in edema and in x-ray scores) as compared with untreated control rats.

As another, alternative example, Groups 2 and 3 are dosed daily with morphogen beginning on Day 18 and continuing through Day 50 to demonstrate the efficacy of morphogens in arthritic animals.

Example 12. Morphogen Inhibition of Localized Edema

The following example demonstrates morphogen efficacy in inhibiting a localized inflammatory response in a standard rat edema model. Experimental rats (e.g., Long-Evans from Charles River Laboratories, Wilmington, MA) are divided into three groups: Group 1, a negative control, which receives vehicle alone; Group 2, a positive control, to which is administered a well-known characterized anti-inflammatory agent (e.g., indomethacin), and Group 3, to which morphogen is provided.

Groups 2 and 3 may be further subdivided to test low, medium and high doses (e.g., Group 2: 1.0 mg/kg, 3.0 mg/kg and 9.0 mg/kg indomethacin; Group 3: 0.1-5µg;

5-20 μ g, and 20-50 μ g of morphogen). Sixty minutes after indomethacin or morphogen is provided to the rats of Group 2 or 3 (e.g., as by injection into the tail vein, or by oral gavage) inflammation is induced in all rats by a sub-plantar injection of a 1% carrageenin solution (50 μ l) into the right hind paw. Three hours after carrageenin administration paw thickness is measured as an indication of edema (e.g., swelling) and induced inflammatory response to the injected carrageenin solution.

Significant swelling is evident in untreated rats by three hours after carrageenin injection. Inflammation also is measured by histology by standard means, following euthanasia e.g.: the right hind paw from each animal is removed at the ankle joint and weighed and foot pad tissue is fixed in 10% neutral buffered formalin, and slides prepared for visual examination by staining the prepared tissue with hematoxylin and eosin.

The morphogen-treated rats show substantially reduced edema induction following carrageenin injection as compared with the untreated rats.

Example 13. Morphogen Treatment of Allergic Encephalomyelitis

The following example demonstrates morphogen efficacy in treating experimental allergic encephalomyelitis (EAE) in a rat. EAE is a well-characterized animal model for multiple sclerosis, an autoimmune disease. A detailed description of the protocol is disclosed in Kuruvilla, et al., (1991) PNAS 88:2918-2921, the disclosure of which is incorporated

herein by reference.

Briefly, EAE is induced in rats (e.g., Long-Evans, Charles River Laboratories, Wilmington, MA) by
5 injection of a CNS tissue (e.g., spinal cord)
homogenate in complete Freund's adjuvant (CFA) on days
-44, -30 and 0 (last day of immunization), by
subcutaneous injection to three sites on the animal's
back. Morphogen is administered daily by
10 interperitoneal injection beginning on day -31.
Preferably, a series of morphogen dose ranges is
evaluated (e.g., low, medium and high) as for
Example 12, above.) Control rats receive morphogen
vehicle only (e.g. 0.9% NaCl or buffered saline). Rats
15 are examined daily for signs of disease and graded on
an increasing severity scale of 0-4.

In the absence of morphogen treatment, significant
neurological dysfunction (e.g., hind and fore limb
20 weakness, progressing to total hind limb paralysis) is
evident by day +7 to +10. Hematology, serum chemistry
profiles and histology are performed to evaluate the
degree of tissue necropsy using standard procedures.
Morphogen treatment significantly inhibits the
25 neurological dysfunction normally evident in an EAE
animal. In addition, the histopathological markers
typically associated with EAE are absent in the
morphogen-treated animals.

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Example 14. Morphogen Treatment of Collagen-Induced Arthritis

The following example demonstrates the efficacy of
35 morphogens in inhibiting the inflammatory response in a

collagen-induced arthritis (CIA) in a rat. CIA is a well-characterized animal model for rheumatoid arthritis, an autoimmune disease. The protocol disclosed is essentially that disclosed in Kuruvilla et al., (1991) PNAS 88:2918-2921, incorporated by reference hereinabove. Briefly, CIA is induced in experimental rats (e.g., Long-Evans, Charles River Laboratories, Wilmington), by multiple intradermal injection of bovine Type II collagen (e.g., 100 μ g) in CFA (0.2 ml) on Day 1. Animals are divided into two groups: Group 1, control animals, which receive vehicle alone, and Group 2: morphogen-treated animals, which, preferably, are subdivided into low, medium and high dose ranges, as described for Example 13, above. Morphogen is administered daily (e.g., by tail vein injection) beginning at different times following collagen injection, e.g., beginning on day 7, 14, 28, 35 and 42. Animals are evaluated visually and paw thickness and body weight is monitored throughout the experiment. Animals are sacrificed on day 60 and the proximal and distal limb joints, and ear, tail and spinal cord prepared for histological evaluation as described for Examples 12 and 13, above. In a variation of the experiment, morphogen may be administered for prescribed periods, e.g., five day periods, beginning at different times following collagen injection (e.g., on days 0-4, 7-11, 14-18, 28-32.)

In the absence of morphogen treatment, an arthritic condition typically is induced by 30 days post collagen injection. In morphogen-treated animals, CIA is suppressed and the histopathological changes typically evidenced in control CIA-induced animals are absent: e.g., accumulations of activated mononuclear

inflammatory cells and fibrous connective tissue. In addition, consistent with the results in Example 7, above, serum anti-collagen antibody titers are suppressed significantly in the morphogen-treated animals.

Example 15. Screening Assay for Candidate Compounds which Alter Endogenous Morphogen Levels

10 Candidate compound(s) which may be administered to affect the level of a given morphogen may be found using the following screening assay, in which the level of morphogen production by a cell type which produces measurable levels of the morphogen is determined with and without incubating the cell in culture with the compound, in order to assess the effects of the compound on the cell. This can be accomplished by detection of the morphogen either at the protein or RNA level. A more detailed description also may be found in USSN 752,861, incorporated hereinabove by reference.

15.1 Growth of Cells in Culture

Cell cultures of kidney, adrenals, urinary bladder, brain, or other organs, may be prepared as described widely in the literature. For example, kidneys may be explanted from neonatal or new born or young or adult rodents (mouse or rat) and used in organ culture as whole or sliced (1-4 mm) tissues. Primary tissue cultures and established cell lines, also derived from kidney, adrenals, urinary, bladder, brain, mammary, or other tissues may be established in multiwell plates (6 well or 24 well) according to conventional cell culture techniques, and are cultured in the absence or presence of serum for a period of time (1-7 days). Cells may be

cultured, for example, in Dulbecco's Modified Eagle medium (Gibco, Long Island, NY) containing serum (e.g., fetal calf serum at 1%-10%, Gibco) or in serum-deprived medium, as desired, or in defined medium (e.g.,
5 containing insulin, transferrin, glucose, albumin, or other growth factors).

Samples for testing the level of morphogen production includes culture supernatants or cell
10 lysates, collected periodically and evaluated for OP-1 production by immunoblot analysis (Sambrook et al., eds., 1989, Molecular Cloning, Cold Spring Harbor Press, Cold Spring Harbor, NY), or a portion of the cell culture itself, collected periodically and used to
15 prepare polyA+ RNA for RNA analysis. To monitor de novo OP-1 synthesis, some cultures are labeled according to conventional procedures with an ^{35}S -methionine/ ^{35}S -cysteine mixture for 6-24 hours and then evaluated to OP-1 synthesis by conventional
20 immunoprecipitation methods.

15.2 Determination of Level of Morphogenic Protein

In order to quantitate the production of a
25 morphogenic protein by a cell type, an immunoassay may be performed to detect the morphogen using a polyclonal or monoclonal antibody specific for that protein. For example, OP-1 may be detected using a polyclonal antibody specific for OP-1 in an ELISA, as follows.

30 1 $\mu\text{g}/100 \mu\text{l}$ of affinity-purified polyclonal rabbit IgG specific for OP-1 is added to each well of a 96-well plate and incubated at 37°C for an hour. The wells are washed four times with 0.167M sodium borate buffer with 0.15 M NaCl (BSB), pH 8.2, containing 0.1%
35

Tween 20. To minimize non-specific binding, the wells are blocked by filling completely with 1% bovine serum albumin (BSA) in BSB and incubating for 1 hour at 37°C. The wells are then washed four times with BSB containing 0.1% Tween 20. A 100 μ l aliquot of an appropriate dilution of each of the test samples of cell culture supernatant is added to each well in triplicate and incubated at 37°C for 30 min. After incubation, 100 μ l biotinylated rabbit anti-OP-1 serum (stock solution is about 1 mg/ml and diluted 1:400 in BSB containing 1% BSA before use) is added to each well and incubated at 37°C for 30 min. The wells are then washed four times with BSB containing 0.1% Tween 20. 100 μ l streptavidin-alkaline (Southern Biotechnology Associates, Inc. Birmingham, Alabama, diluted 1:2000 in BSB containing 0.1% Tween 20 before use) is added to each well and incubated at 37°C for 30 min. The plates are washed four times with 0.5M Tris buffered Saline (TBS), pH 7.2. 50 μ l substrate (ELISA Amplification System Kit, Life Technologies, Inc., Bethesda, MD) is added to each well incubated at room temperature for 15 min. Then, 50 μ l amplifier (from the same amplification system kit) is added and incubated for another 15 min at room temperature. The reaction is stopped by the addition of 50 μ l 0.3 M sulphuric acid. The OD at 490 nm of the solution in each well is recorded. To quantitate OP-1 in culture media, a OP-1 standard curve is performed in parallel with the test samples.

30

Polyclonal antibody may be prepared as follows.

Each rabbit is given a primary immunization of 100 μ g/500 μ l E. coli produced OP-1 monomer (amino acids 328-431 in SEQ ID NO:5) in 0.1% SDS mixed with 500 μ l

35 Complete Freund's Adjuvant. The antigen is injected

subcutaneously at multiple sites on the back and flanks of the animal. The rabbit is boosted after a month in the same manner using incomplete Freund's Adjuvant. Test bleeds are taken from the ear vein seven days later. Two additional boosts and test bleeds are performed at monthly intervals until antibody against OP-1 is detected in the serum using an ELISA assay. Then, the rabbit is boosted monthly with 100 μ g of antigen and bled (15 ml per bleed) at days seven and ten after boosting.

Monoclonal antibody specific for a given morphogen may be prepared as follows. A mouse is given two injections of E. coli produced OP-1 monomer. The first injection contains 100 μ g of OP-1 in complete Freund's adjuvant and is given subcutaneously. The second injection contains 50 μ g of OP-1 in incomplete adjuvant and is given intraperitoneally. The mouse then receives a total of 230 μ g of OP-1 (amino acids 307-431 in SEQ ID NO:5) in four intraperitoneal injections at various times over an eight month period. One week prior to fusion, both mice are boosted intraperitoneally with 100 μ g of OP-1 (307-431) and 30 μ g of the N-terminal peptide (Ser₂₉₃-Asn₃₀₉-Cys) conjugated through the added cysteine to bovine serum albumin with SMCC crosslinking agent. This boost was repeated five days (IP), four days (IP), three days (IP) and one day (IV) prior to fusion. The mouse spleen cells are then fused to myeloma (e.g., 653) cells at a ratio of 1:1 using PEG 1500 (Boehringer Mannheim), and the cell fusion is plated and screened for OP-1-specific antibodies using OP-1 (307-431) as antigen. The cell fusion and monoclonal screening then are according to standard procedures well described in standard texts widely available in the art.

The invention may be embodied in other specific forms without departing from the spirit or essential characteristics thereof. The present embodiments are therefore to be considered in all respects as illustrative and not restrictive, the scope of the invention being indicated by the appended claims rather than by the foregoing description, and all changes which come within the meaning and range of equivalency of the claims are therefore intended to be embraced therein.

[illegible]

SEQUENCE LISTING

(1) GENERAL INFORMATION:

(i) APPLICANT: KUBERASAMPATH, THANGAVEL
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(ii) TITLE OF INVENTION: MORPHOGEN-INDUCED MODULATION OF
INFLAMMATORY RESPONSE

(iii) NUMBER OF SEQUENCES: 33

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(F) ZIP:

(v) COMPUTER READABLE FORM:

(A) MEDIUM TYPE: Floppy disk
(B) COMPUTER: IBM PC compatible
(C) OPERATING SYSTEM: PC-DOS/MS-DOS
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(2) INFORMATION FOR SEQ ID # NO:1:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 97 amino acids
(B) TYPE: amino acids
(C) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(ix) FEATURE:

(A) NAME: Generic Sequence 1

000290" 4756560

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:
Xaa Xaa Xaa Xaa Xaa Xaa

(2) INFORMATION FOR SEQ ID NO:2:

(D) OTHER INFORMATION: Each Xaa indicates one of the 20 naturally-occurring L-isomer, α -amino acids or a derivative thereof.

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

[illegible]

[illegible]

(2) INFORMATION FOR SEQ ID NO:3:

- ```
(i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 97 amino acids
 (B) TYPE: amino acids
 (C) TOPOLOGY: linear
(ii) MOLECULE TYPE: protein
(ix) FEATURE:
 (A) NAME: Generic Sequence 3
 (D) OTHER INFORMATION: wherein each
 Xaa is independently selected from
 a group of one or more specified
 amino acids as defined in the
 specification.
```

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

|     | Leu | Tyr | Val | Xaa | Phe |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|
|     | 1   |     |     |     | 5   |     |     |     |
| Xaa | Xaa | Xaa | Gly | Trp | Xaa | Xaa | Trp | Xaa |
|     |     |     |     | 10  |     |     |     |     |
| Xaa | Ala | Pro | Gly | Xaa | Xaa | Xaa | Ala |     |
| 15  |     |     |     |     | 20  |     |     |     |
| Xaa | Tyr | Cys | Xaa | Gly | Xaa | Cys | Xaa |     |
|     |     | 25  |     |     |     |     | 30  |     |
| Xaa | Pro | Xaa | Xaa | Xaa | Xaa | Xaa |     |     |
|     |     |     |     | 35  |     |     |     |     |
| Xaa | Xaa | Xaa | Asn | His | Ala | Xaa | Xaa |     |
|     |     | 40  |     |     |     |     | 45  |     |
| Xaa | Xaa | Leu | Xaa | Xaa | Xaa | Xaa | Xaa |     |
|     |     |     |     | 50  |     |     |     |     |
| Xaa | Xaa | Xaa | Xaa | Xaa | Xaa | Xaa | Cys |     |
|     | 55  |     |     |     |     | 60  |     |     |
| Cys | Xaa | Pro | Xaa | Xaa | Xaa | Xaa | Xaa |     |
|     |     |     | 65  |     |     |     |     |     |
| Xaa | Xaa | Xaa | Leu | Xaa | Xaa | Xaa |     |     |
| 70  |     |     |     |     | 75  |     |     |     |
| Xaa | Xaa | Xaa | Xaa | Val | Xaa | Leu | Xaa |     |
|     |     |     | 80  |     |     |     |     |     |
| Xaa | Xaa | Xaa | Xaa | Met | Xaa | Val | Xaa |     |
| 85  |     |     |     |     | 90  |     |     |     |
| Xaa | Cys | Gly | Cys | Xaa |     |     |     |     |
|     |     | 95  |     |     |     |     |     |     |

(2) INFORMATION FOR SEQ ID NO:4:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 102 amino acids
  - (B) TYPE: amino acids
  - (C) TOPOLOGY: linear
- (ii) MOLECULE TYPE: protein
- (ix) FEATURE:
  - (A) NAME: Generic Sequence 4
  - (D) OTHER INFORMATION: wherein each Xaa is independently selected from a group of one or more specified amino acids as defined in the specification.

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

Cys Xaa Xaa Xaa Xaa Leu Tyr Val Xaa Phe  
1 5 10  
Xaa Xaa Xaa Gly Trp Xaa Xaa Trp Xaa  
15  
Xaa Ala Pro Xaa Gly Xaa Xaa Ala  
20 25  
Xaa Tyr Cys Xaa Gly Xaa Cys Xaa  
30 35  
Xaa Pro Xaa Xaa Xaa Xaa Xaa  
40  
Asn Xaa Xaa Asn His Ala Xaa Xaa  
45 50  
Xaa Xaa Leu Xaa Xaa Xaa Xaa Xaa  
55  
Xaa Xaa Xaa Xaa Xaa Xaa Xaa Cys  
60 65  
Cys Xaa Pro Xaa Xaa Xaa Xaa Xaa  
70  
Xaa Xaa Xaa Leu Xaa Xaa Xaa  
75 80  
Xaa Xaa Xaa Xaa Val Xaa Leu Xaa  
85  
Xaa Xaa Xaa Xaa Met Xaa Val Xaa  
90 95  
Xaa Cys Gly Cys Xaa  
100

(2) INFORMATION FOR SEQ ID NO:5:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 139 amino acids
  - (B) TYPE: amino acids
  - (C) TOPOLOGY: linear
- (ii) MOLECULE TYPE: protein
- (ix) FEATURE:
  - (A) NAME: hOP-1 (mature form)
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

000290-062000

|     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ser | Thr | Gly | Ser | Lys | Gln | Arg | Ser | Gln |
| 1   |     |     |     | 5   |     |     |     |     |
| Asn | Arg | Ser | Lys | Thr | Pro | Lys | Asn | Gln |
| 10  |     |     |     |     | 15  |     |     |     |
| Glu | Ala | Leu | Arg | Met | Ala | Asn | Val | Ala |
|     | 20  |     |     |     |     | 25  |     |     |
| Glu | Asn | Ser | Ser | Ser | Asp | Gln | Arg | Gln |
|     |     | 30  |     |     |     |     | 35  |     |
| Ala | Cys | Lys | Lys | His | Glu | Leu | Tyr | Val |
|     |     |     | 40  |     |     |     |     | 45  |
| Ser | Phe | Arg | Asp | Leu | Gly | Trp | Gln | Asp |
|     |     |     |     | 50  |     |     |     |     |
| Trp | Ile | Ile | Ala | Pro | Glu | Gly | Tyr | Ala |
| 55  |     |     |     |     | 60  |     |     |     |
| Ala | Tyr | Tyr | Cys | Glu | Gly | Glu | Cys | Ala |
|     | 65  |     |     |     |     | 70  |     |     |
| Phe | Pro | Leu | Asn | Ser | Tyr | Met | Asn | Ala |
|     |     | 75  |     |     |     |     | 80  |     |
| Thr | Asn | His | Ala | Ile | Val | Gln | Thr | Leu |
|     |     |     | 85  |     |     |     |     | 90  |
| Val | His | Phe | Ile | Asn | Pro | Glu | Thr | Val |
|     |     |     |     | 95  |     |     |     |     |
| Pro | Lys | Pro | Cys | Cys | Ala | Pro | Thr | Gln |
| 100 |     |     |     |     | 105 |     |     |     |
| Leu | Asn | Ala | Ile | Ser | Val | Leu | Tyr | Phe |
|     | 110 |     |     |     |     | 115 |     |     |
| Asp | Asp | Ser | Ser | Asn | Val | Ile | Leu | Lys |
|     |     | 120 |     |     |     |     | 125 |     |
| Lys | Tyr | Arg | Asn | Met | Val | Val | Arg | Ala |
|     |     |     | 130 |     |     |     |     | 135 |
| Cys | Gly | Cys | His |     |     |     |     |     |

(2)

INFORMATION FOR SEQ ID NO:6:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 139 amino acids

(B) TYPE: amino acids

(C) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(ix) FEATURE:

(A) NAME: mOP-1 (mature form)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

|     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ser | Thr | Gly | Gly | Lys | Gln | Arg | Ser | Gln |
| 1   |     |     |     | 5   |     |     |     |     |
| Asn | Arg | Ser | Lys | Thr | Pro | Lys | Asn | Gln |
| 10  |     |     |     |     | 15  |     |     |     |
| Glu | Ala | Leu | Arg | Met | Ala | Ser | Val | Ala |
|     | 20  |     |     |     |     | 25  |     |     |
| Glu | Asn | Ser | Ser | Ser | Asp | Gln | Arg | Gln |
|     |     | 30  |     |     |     |     | 35  |     |
| Ala | Cys | Lys | Lys | His | Glu | Leu | Tyr | Val |
|     |     |     | 40  |     |     |     |     | 45  |

|     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ser | Phe | Arg | Asp | Leu | Gly | Trp | Gln | Asp |
|     |     |     |     | 50  |     |     |     |     |
| Trp | Ile | Ile | Ala | Pro | Glu | Gly | Tyr | Ala |
| 55  |     |     |     |     | 60  |     |     |     |
| Ala | Tyr | Tyr | Cys | Glu | Gly | Glu | Cys | Ala |
|     | 65  |     |     |     |     | 70  |     |     |
| Phe | Pro | Leu | Asn | Ser | Tyr | Met | Asn | Ala |
|     |     | 75  |     |     |     |     | 80  |     |
| Thr | Asn | His | Ala | Ile | Val | Gln | Thr | Leu |
|     |     |     | 85  |     |     |     |     | 90  |
| Val | His | Phe | Ile | Asn | Pro | Asp | Thr | Val |
|     |     |     |     | 95  |     |     |     |     |
| Pro | Lys | Pro | Cys | Cys | Ala | Pro | Thr | Gln |
| 100 |     |     |     |     | 105 |     |     |     |
| Leu | Asn | Ala | Ile | Ser | Val | Leu | Tyr | Phe |
|     | 110 |     |     |     |     | 115 |     |     |
| Asp | Asp | Ser | Ser | Asn | Val | Ile | Leu | Lys |
|     |     | 120 |     |     |     |     | 125 |     |
| Lys | Tyr | Arg | Asn | Met | Val | Val | Arg | Ala |
|     |     |     | 130 |     |     |     |     | 135 |
| Cys | Gly | Cys | His |     |     |     |     |     |

(2)

INFORMATION FOR SEQ ID NO:7:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 139 amino acids
  - (B) TYPE: amino acids
  - (C) TOPOLOGY: linear
- (ii) MOLECULE TYPE: protein
- (ix) FEATURE:
  - (A) NAME: hOP-2 (mature form)
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

|     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ala | Val | Arg | Pro | Leu | Arg | Arg | Arg | Gln |
| 1   |     |     |     | 5   |     |     |     |     |
| Pro | Lys | Lys | Ser | Asn | Glu | Leu | Pro | Gln |
| 10  |     |     |     |     | 15  |     |     |     |
| Ala | Asn | Arg | Leu | Pro | Gly | Ile | Phe | Asp |
|     | 20  |     |     |     |     | 25  |     |     |
| Asp | Val | His | Gly | Ser | His | Gly | Arg | Gln |
|     |     | 30  |     |     |     |     | 35  |     |
| Val | Cys | Arg | Arg | His | Glu | Leu | Tyr | Val |
|     |     |     | 40  |     |     |     |     | 45  |
| Ser | Phe | Gln | Asp | Leu | Gly | Trp | Leu | Asp |
|     |     |     |     | 50  |     |     |     |     |
| Trp | Val | Ile | Ala | Pro | Gln | Gly | Tyr | Ser |
| 55  |     |     |     |     | 60  |     |     |     |
| Ala | Tyr | Tyr | Cys | Glu | Gly | Glu | Cys | Ser |
|     | 65  |     |     |     |     | 70  |     |     |
| Phe | Pro | Leu | Asp | Ser | Cys | Met | Asn | Ala |
|     |     | 75  |     |     |     |     | 80  |     |
| Thr | Asn | His | Ala | Ile | Leu | Gln | Ser | Leu |
|     |     |     | 85  |     |     |     |     | 90  |
| Val | His | Leu | Met | Lys | Pro | Asn | Ala | Val |

INFORMATION FOR SEQ ID NO:8:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 139 amino acids
  - (B) TYPE: amino acids
  - (C) TOPOLOGY: linear
- (ii) MOLECULE TYPE: protein
- (ix) FEATURE:
  - (A) NAME: mOP-2 (mature form)
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

|            |            |            |            |           |            |            |            |            |
|------------|------------|------------|------------|-----------|------------|------------|------------|------------|
| Ala<br>1   | Ala        | Arg        | Pro        | Leu<br>5  | Lys        | Arg        | Arg        | Gln        |
| Pro<br>10  | Lys        | Lys        | Thr        | Asn       | Glu<br>15  | Leu        | Pro        | His        |
| Pro<br>20  | Asn        | Lys        | Leu        | Pro       | Gly        | Ile<br>25  | Phe        | Asp        |
| Asp        | Gly        | His<br>30  | Gly        | Ser       | Arg        | Gly        | Arg<br>35  | Glu        |
| Val        | Cys        | Arg        | Arg<br>40  | His       | Glu        | Leu        | Tyr        | Val<br>45  |
| Ser        | Phe        | Arg        | Asp        | Leu<br>50 | Gly        | Trp        | Leu        | Asp        |
| Trp<br>55  | Val        | Ile        | Ala        | Pro       | Gln<br>60  | Gly        | Tyr        | Ser        |
| Ala<br>65  | Tyr        | Tyr        | Cys        | Glu       | Gly        | Glu<br>70  | Cys        | Ala        |
| Phe        | Pro        | Leu<br>75  | Asp        | Ser       | Cys        | Met        | Asn<br>80  | Ala        |
| Thr        | Asn        | His        | Ala<br>85  | Ile       | Leu        | Gln        | Ser        | Leu<br>90  |
| Val        | His        | Leu        | Met        | Lys<br>95 | Pro        | Asp        | Val        | Val        |
| Pro<br>100 | Lys        | Ala        | Cys        | Cys       | Ala<br>105 | Pro        | Thr        | Lys        |
| Leu        | Ser<br>110 | Ala        | Thr        | Ser       | Val        | Leu<br>115 | Tyr        | Tyr        |
| Asp        | Ser        | Ser<br>120 | Asn        | Asn       | Val        | Ile        | Leu<br>125 | Arg        |
| Lys        | His        | Arg        | Asn<br>130 | Met       | Val        | Val        | Lys        | Ala<br>135 |
| Cys        | Gly        | Cys        | His        |           |            |            |            |            |



(2)

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INFORMATION FOR SEQ ID NO:
(i) SEQUENCE CHARACTERISTICS:
    (A) LENGTH: 96 amino acids
    (B) TYPE: amino acids
    (C) TOPOLOGY: linear
(ii) MOLECULE TYPE: protein
(ix) FEATURE:
    (A) NAME: CBMP-2A(fx)
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

```

[illegible]

(2)

- ```

INFORMATION FOR SEQ ID NO:10:
(i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 101 amino acids
 (B) TYPE: amino acids
 (C) TOPOLOGY: linear
(ii) MOLECULE TYPE: protein
(ix) FEATURE:
 (A) NAME: CBMP-2B(fx)
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

```

|           |           |           |     |           |           |           |           |           |           |           |
|-----------|-----------|-----------|-----|-----------|-----------|-----------|-----------|-----------|-----------|-----------|
|           |           |           |     |           |           | Cys<br>1  | Arg       | Arg       | His       | Ser<br>5  |
| Leu       | Tyr       | Val       | Asp | Phe<br>10 | Ser       | Asp       | Val       | Gly       | Trp<br>15 | Asn       |
| Asp       | Trp       | Ile       | Val | Ala<br>20 | Pro       | Pro       | Gly       | Tyr<br>25 | Gln       | Ala       |
| Phe       | Tyr       | Cys<br>30 | His | Gly       | Asp       | Cys       | Pro<br>35 | Phe       | Pro       | Leu       |
| Ala       | Asp<br>40 | His       | Leu | Asn       | Ser       | Thr<br>45 | Asn       | His       | Ala       | Ile       |
| Val<br>50 | Gln       | Thr       | Leu | Val       | Asn<br>55 | Ser       | Val       | Asn       | Ser       | Ser<br>60 |

(2) INFORMATION FOR SEQ ID NO:11:  
 (i) SEQUENCE CHARACTERISTICS:  
     (A) LENGTH: 102 amino acids  
     (B) TYPE: amino acids  
     (C) TOPOLOGY: linear  
 (ii) MOLECULE TYPE: protein  
 (ix) FEATURE:  
     (A) NAME: DPP(fx)  
 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

(2) INFORMATION FOR SEQ ID NO:12:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 102 amino acids
  - (B) TYPE: amino acids
  - (C) TOPOLOGY: linear
- (ii) MOLECULE TYPE: protein
- (ix) FEATURE:
  - (A) NAME: Vgl(fx)
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

Cys Lys Lys Arg His Leu Tyr Val Glu Phe Lys  
1 5 10  
Asp Val Gly Trp Gln Asn Trp Val Ile Ala Pro

```

 15 20
Gln Gly Tyr Met Ala Asn Tyr Cys Tyr Gly Glu
 25 30
Cys Pro Tyr Pro Leu Thr Glu Ile Leu Asn Gly
 35 40
Ser Asn His Ala Ile Leu Gln Thr Leu Val His
 45 50 55
Ser Ile Glu Pro Glu Asp Ile Pro Leu Pro Cys
 60 65
Cys Val Pro Thr Lys Met Ser Pro Ile Ser Met
 70 75
Leu Phe Tyr Asp Asn Asn Asp Asn Val Val Leu
 80 85
Arg His Tyr Glu Asn Met Ala Val Asp Glu Cys
 90 95
Gly Cys Arg
100

```

(2)

INFORMATION FOR SEQ ID NO:13:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 102 amino acids
  - (B) TYPE: amino acids
  - (C) TOPOLOGY: linear
- (ii) MOLECULE TYPE: protein
- (ix) FEATURE:
  - (A) NAME: Vgr-1(fx)
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

```

Cys Lys Lys His Glu Leu Tyr Val Ser Phe Gln
 1 5 10
Asp Val Gly Trp Gln Asp Trp Ile Ile Ala Pro
 15 20
Xaa Gly Tyr Ala Ala Asn Tyr Cys Asp Gly Glu
 25 30
Cys Ser Phe Pro Leu Asn Ala His Met Asn Ala
 35 40
Thr Asn His Ala Ile Val Gln Thr Leu Val His
 45 50 55
Val Met Asn Pro Glu Tyr Val Pro Lys Pro Cys
 60 65
Cys Ala Pro Thr Lys Val Asn Ala Ile Ser Val
 70 75
Leu Tyr Phe Asp Asp Asn Ser Asn Val Ile Leu
 80 85
Lys Lys Tyr Arg Asn Met Val Val Arg Ala Cys
 90 95
Gly Cys His
100

```

(2) INFORMATION FOR SEQ ID NO:14:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 106 amino acids

(vi) ORIGINAL SOURCE:  
(A) ORGANISM: human  
(F) TISSUE TYPE: BRAIN

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

(2) INFORMATION FOR SEQ ID NO:15:

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

Cys Xaa Xaa Xaa Xaa  
1 5

(2) INFORMATION FOR SEQ ID NO:16:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1822 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(vi) ORIGINAL SOURCE:

- (A) ORGANISM: HOMO SAPIENS
- (F) TISSUE TYPE: HIPPOCAMPUS

(ix) FEATURE:

- (A) NAME/KEY: CDS
- (B) LOCATION: 49..1341
- (D) OTHER INFORMATION:/standard\_name= "hOP1"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:

|                                                                  |     |
|------------------------------------------------------------------|-----|
| GGTGCGGGCC CGGAGCCCGG AGCCCGGGTA GCGCGTAGAG CCGGCGCG ATG CAC GTG | 57  |
| Met His Val                                                      |     |
| 1                                                                |     |
| CGC TCA CTG CGA GCT GCG GCG CCG CAC AGC TTC GTG GCG CTC TGG GCA  | 105 |
| Arg Ser Leu Arg Ala Ala Ala Pro His Ser Phe Val Ala Leu Trp Ala  |     |
| 5 10 15                                                          |     |
| CCC CTG TTC CTG CTG CGC TCC GCC CTG GCC GAC TTC AGC CTG GAC AAC  | 153 |
| Pro Leu Phe Leu Leu Arg Ser Ala Leu Ala Asp Phe Ser Leu Asp Asn  |     |
| 20 25 30 35                                                      |     |
| GAG GTG CAC TCG AGC TTC ATC CAC CGG CGC CTC CGC AGC CAG GAG CGG  | 201 |
| Glu Val His Ser Ser Phe Ile His Arg Arg Leu Arg Ser Gln Glu Arg  |     |
| 40 45 50                                                         |     |
| CGG GAG ATG CAG CGC GAG ATC CTC TCC ATT TTG GGC TTG CCC CAC CGC  | 249 |
| Arg Glu Met Gln Arg Glu Ile Leu Ser Ile Leu Gly Leu Pro His Arg  |     |
| 55 60 65                                                         |     |
| CCG CGC CCG CAC CTC CAG GGC AAG CAC AAC TCG GCA CCC ATG TTC ATG  | 297 |
| Pro Arg Pro His Leu Gln Gly Lys His Asn Ser Ala Pro Met Phe Met  |     |
| 70 75 80                                                         |     |
| CTG GAC CTG TAC AAC GCC ATG GCG GTG GAG GAG GGC GGC GGG CCC GGC  | 345 |
| Leu Asp Leu Tyr Asn Ala Met Ala Val Glu Glu Gly Gly Gly Pro Gly  |     |
| 85 90 95                                                         |     |
| GGC CAG GGC TTC TCC TAC CCC TAC AAG GCC GTC TTC AGT ACC CAG GGC  | 393 |
| Gly Gln Gly Phe Ser Tyr Pro Tyr Lys Ala Val Phe Ser Thr Gln Gly  |     |
| 100 105 110 115                                                  |     |

|                   |                   |                   |                   |                   |                   |                   |                   |                   |                   |                   |                   |                   |                   |                   |                   |      |
|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|------|
| CCC<br>Pro        | CCT<br>Pro        | CTG<br>Leu        | GCC<br>Ala        | AGC<br>Ser<br>120 | CTG<br>Leu        | CAA<br>Gln        | GAT<br>Asp        | AGC<br>Ser        | CAT<br>His<br>125 | TTC<br>Phe        | CTC<br>Leu        | ACC<br>Thr        | GAC<br>Asp        | GCC<br>Ala<br>130 | GAC<br>Asp        | 441  |
| ATG<br>Met        | GTC<br>Val        | ATG<br>Met        | AGC<br>Ser<br>135 | TTC<br>Phe        | GTC<br>Val        | AAC<br>Asn        | CTC<br>Leu        | GTG<br>Val<br>140 | GAA<br>Glu        | CAT<br>His        | GAC<br>Asp        | AAG<br>Lys        | GAA<br>Glu<br>145 | TTC<br>Phe        | TTC<br>Phe        | 489  |
| CAC<br>His        | CCA<br>Pro        | CGC<br>Arg<br>150 | TAC<br>Tyr        | CAC<br>His        | CAT<br>His        | CGA<br>Arg        | GAG<br>Glu<br>155 | TTC<br>Phe        | CGG<br>Arg        | TTT<br>Phe        | GAT<br>Asp        | CTT<br>Leu<br>160 | TCC<br>Ser        | AAG<br>Lys        | ATC<br>Ile        | 537  |
| CCA<br>Pro        | GAA<br>Glu<br>165 | GGG<br>Gly        | GAA<br>Glu        | GCT<br>Ala        | GTC<br>Val        | ACG<br>Thr<br>170 | GCA<br>Ala        | GCC<br>Ala        | GAA<br>Glu        | TTC<br>Phe        | CGG<br>Arg<br>175 | ATC<br>Ile        | TAC<br>Tyr        | AAG<br>Lys        | GAC<br>Asp        | 585  |
| TAC<br>Tyr<br>180 | ATC<br>Ile        | CGG<br>Arg        | GAA<br>Glu        | CGC<br>Arg        | TTC<br>Phe<br>185 | GAC<br>Asp        | AAT<br>Asn        | GAG<br>Glu        | ACG<br>Thr<br>190 | TTC<br>Phe        | CGG<br>Arg        | ATC<br>Ile        | AGC<br>Ser        | GTT<br>Val        | TAT<br>Tyr<br>195 | 633  |
| CAG<br>Gln        | GTG<br>Val        | CTC<br>Leu        | CAG<br>Gln<br>200 | GAG<br>Glu        | CAC<br>His        | TTG<br>Leu        | GGC<br>Gly        | AGG<br>Arg<br>205 | GAA<br>Glu<br>205 | TCG<br>Ser        | GAT<br>Asp        | CTC<br>Leu        | TTC<br>Phe        | CTG<br>Leu<br>210 | CTC<br>Leu        | 681  |
| GAC<br>Asp        | AGC<br>Ser        | CGT<br>Arg<br>215 | ACC<br>Thr        | CTC<br>Leu        | TGG<br>Trp        | GCC<br>Ala        | TCG<br>Ser        | GAG<br>Glu<br>220 | GAG<br>Glu        | GGC<br>Gly        | TGG<br>Trp        | CTG<br>Leu        | GTG<br>Val<br>225 | TTT<br>Phe        | GAC<br>Asp        | 729  |
| ATC<br>Ile        | ACA<br>Thr<br>230 | GCC<br>Ala        | ACC<br>Thr        | AGC<br>Ser        | AAC<br>Asn        | CAC<br>His        | TGG<br>Trp<br>235 | GTG<br>Val        | GTC<br>Val        | AAT<br>Asn        | CCG<br>Pro        | CGG<br>Arg<br>240 | CAC<br>His        | AAC<br>Asn        | CTG<br>Leu        | 777  |
| GGC<br>Gly<br>245 | CTG<br>Leu        | CAG<br>Gln        | CTC<br>Leu        | TCG<br>Ser        | GTG<br>Val        | GAG<br>Glu<br>250 | ACG<br>Thr        | CTG<br>Leu        | GAT<br>Asp        | GGG<br>Gly        | CAG<br>Gln<br>255 | AGC<br>Ser        | ATC<br>Ile        | AAC<br>Asn        | CCC<br>Pro        | 825  |
| AAG<br>Lys<br>260 | TTG<br>Leu        | GCG<br>Ala        | GGC<br>Gly        | CTG<br>Leu        | ATT<br>Ile<br>265 | GGG<br>Gly        | CGG<br>Arg        | CAC<br>His        | GGG<br>Gly        | CCC<br>Pro<br>270 | CAG<br>Gln        | AAC<br>Asn        | AAG<br>Lys        | CAG<br>Gln        | CCC<br>Pro<br>275 | 873  |
| TTC<br>Phe        | ATG<br>Met        | GTG<br>Val        | GCT<br>Ala<br>280 | TTC<br>Phe        | TTC<br>Phe        | AAG<br>Lys        | GCC<br>Ala        | ACG<br>Thr<br>285 | GAG<br>Glu        | GTC<br>Val        | CAC<br>His        | TTC<br>Phe        | CGC<br>Arg<br>290 | AGC<br>Ser        | ATC<br>Ile        | 921  |
| CGG<br>Arg        | TCC<br>Ser        | ACG<br>Thr<br>295 | GGG<br>Gly        | AGC<br>Ser        | AAA<br>Lys        | CAG<br>Gln        | CGC<br>Arg        | AGC<br>Ser<br>300 | CAG<br>Gln        | AAC<br>Asn        | CGC<br>Arg        | TCC<br>Ser<br>305 | AAG<br>Lys        | ACG<br>Thr        | CCC<br>Pro        | 969  |
| AAG<br>Lys        | AAC<br>Asn<br>310 | CAG<br>Gln        | GAA<br>Glu        | GCC<br>Ala        | CTG<br>Leu        | CGG<br>Arg<br>315 | ATG<br>Met        | GCC<br>Ala        | AAC<br>Asn        | GTG<br>Val        | GCA<br>Ala<br>320 | GAG<br>Glu        | AAC<br>Asn        | AGC<br>Ser        | AGC<br>Ser        | 1017 |

|                                                                                                                                                       |      |
|-------------------------------------------------------------------------------------------------------------------------------------------------------|------|
| AGC GAC CAG AGG CAG GCC TGT AAG AAG CAC GAG CTG TAT GTC AGC TTC<br>Ser Asp Gln Arg Gln Ala Cys Lys Lys His Glu Leu Tyr Val Ser Phe<br>325 330 335     | 1065 |
| CGA GAC CTG GGC TGG CAG GAC TGG ATC ATC GCG CCT GAA GGC TAC GCC<br>Arg Asp Leu Gly Trp Gln Asp Trp Ile Ile Ala Pro Glu Gly Tyr Ala<br>340 345 350 355 | 1113 |
| GCC TAC TAC TGT GAG GGG CAG TGT GCC TTC CCT CTG AAC TCC TAC ATG<br>Ala Tyr Tyr Cys Glu Gly Glu Cys Ala Phe Pro Leu Asn Ser Tyr Met<br>360 365 370     | 1161 |
| AAC GCC ACC AAC CAC GCC ATC GTG CAG ACG CTG GTC CAC TTC ATC AAC<br>Asn Ala Thr Asn His Ala Ile Val Gln Thr Leu Val His Phe Ile Asn<br>375 380 385     | 1209 |
| CCG GAA ACG GTG CCC AAG CCC TGC TGT GCG CCC ACG CAG CTC AAT GCC<br>Pro Glu Thr Val Pro Lys Pro Cys Cys Ala Pro Thr Gln Leu Asn Ala<br>390 395 400     | 1257 |
| ATC TCC GTC CTC TAC TTC GAT GAC AGC TCC AAC GTC ATC CTG AAG AAA<br>Ile Ser Val Leu Tyr Phe Asp Asp Ser Ser Asn Val Ile Leu Lys Lys<br>405 410 415     | 1305 |
| TAC AGA AAC ATG GTG GTC CGG GCC TGT GGC TGC CAC TAGCTCCTCC<br>Tyr Arg Asn Met Val Val Arg Ala Cys Gly Cys His<br>420 425 430                          | 1351 |
| GAGAATTCAG ACCCTTTGGG GCCAAGTTTT TCTGGATCCT CCATTGCTCG CCTTGGCCAG                                                                                     | 1411 |
| GAACCAGCAG ACCAACTGCC TTTTGTGAGA CCTTCCCCTC CCTATCCCCA ACTTTAAAGG                                                                                     | 1471 |
| TGTGAGAGTA TTAGGAAACA TGAGCAGCAT ATGGCTTTTG ATCAGTTTTT CAGTGGCAGC                                                                                     | 1531 |
| ATCCAATGAA CAAGATCCTA CAAGCTGTGC AGGCAAAACC TAGCAGGAAA AAAAAACAAC                                                                                     | 1591 |
| GCATAAAGAA AAATGGCCGG GCCAGGTCAT TGGCTGGGAA GTCTCAGCCA TGCACGGACT                                                                                     | 1651 |
| CGTTTCCAGA GGTAATTATG AGCGCCTACC AGCCAGGCCA CCCAGCCGTG GGAGGAAGGG                                                                                     | 1711 |
| GGCGTGGCAA GGGGTGGGCA CATTGGTGTC TGTGCGAAAG GAAAATTGAC CCGGAAGTTC                                                                                     | 1771 |
| CTGTAATAAA TGTCAACAATA AAACGAATGA ATGAAAAAAAA AAAAAAAAAA A                                                                                            | 1822 |

(2) INFORMATION FOR SEQ ID NO:17:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 431 amino acids
  - (B) TYPE: amino acid
  - (D) TOPOLOGY: linear

- (ii) MOLECULE TYPE: protein

(ix) FEATURE:  
(D) OTHER INFORMATION: /Product="OP1-PP"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:

Met His Val Arg Ser Leu Arg Ala Ala Ala Pro His Ser Phe Val Ala  
1 5 10 15  
Leu Trp Ala Pro Leu Phe Leu Leu Arg Ser Ala Leu Ala Asp Phe Ser  
20 25 30  
Leu Asp Asn Glu Val His Ser Ser Phe Ile His Arg Arg Leu Arg Ser  
35 40 45  
Gln Glu Arg Arg Glu Met Gln Arg Glu Ile Leu Ser Ile Leu Gly Leu  
50 55 60  
Pro His Arg Pro Arg Pro His Leu Gln Gly Lys His Asn Ser Ala Pro  
65 70 75 80  
Met Phe Met Leu Asp Leu Tyr Asn Ala Met Ala Val Glu Glu Gly Gly  
85 90 95  
Gly Pro Gly Gly Gln Gly Phe Ser Tyr Pro Tyr Lys Ala Val Phe Ser  
100 105 110  
Thr Gln Gly Pro Pro Leu Ala Ser Leu Gln Asp Ser His Phe Leu Thr  
115 120 125  
Asp Ala Asp Met Val Met Ser Phe Val Asn Leu Val Glu His Asp Lys  
130 135 140  
Glu Phe Phe His Pro Arg Tyr His His Arg Glu Phe Arg Phe Asp Leu  
145 150 155 160  
Ser Lys Ile Pro Glu Gly Glu Ala Val Thr Ala Ala Glu Phe Arg Ile  
165 170 175  
Tyr Lys Asp Tyr Ile Arg Glu Arg Phe Asp Asn Glu Thr Phe Arg Ile  
180 185 190  
Ser Val Tyr Gln Val Leu Gln Glu His Leu Gly Arg Glu Ser Asp Leu  
195 200 205  
Phe Leu Leu Asp Ser Arg Thr Leu Trp Ala Ser Glu Glu Gly Trp Leu  
210 215 220  
Val Phe Asp Ile Thr Ala Thr Ser Asn His Trp Val Val Asn Pro Arg  
225 230 235 240  
His Asn Leu Gly Leu Gln Leu Ser Val Glu Thr Leu Asp Gly Gln Ser  
245 250 255



Ile Asn Pro Lys Leu Ala Gly Leu Ile Gly Arg His Gly Pro Gln Asn  
260 265 270

Lys Gln Pro Phe Met Val Ala Phe Phe Lys Ala Thr Glu Val His Phe  
275 280 285

Arg Ser Ile Arg Ser Thr Gly Ser Lys Gln Arg Ser Gln Asn Arg Ser  
290 295 300

Lys Thr Pro Lys Asn Gln Glu Ala Leu Arg Met Ala Asn Val Ala Glu  
305 310 315 320

Asn Ser Ser Ser Asp Gln Arg Gln Ala Cys Lys Lys His Glu Leu Tyr  
325 330 335

Val Ser Phe Arg Asp Leu Gly Trp Gln Asp Trp Ile Ile Ala Pro Glu  
340 345 350

Gly Tyr Ala Ala Tyr Tyr Cys Glu Gly Glu Cys Ala Phe Pro Leu Asn  
355 360 365

Ser Tyr Met Asn Ala Thr Asn His Ala Ile Val Gln Thr Leu Val His  
370 375 380

Phe Ile Asn Pro Glu Thr Val Pro Lys Pro Cys Cys Ala Pro Thr Gln  
385 390 395 400

Leu Asn Ala Ile Ser Val Leu Tyr Phe Asp Asp Ser Ser Asn Val Ile  
405 410 415

Leu Lys Lys Tyr Arg Asn Met Val Val Arg Ala Cys Gly Cys His  
420 425 430

(2) INFORMATION FOR SEQ ID NO:18:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 1873 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: cDNA
- (vi) ORIGINAL SOURCE:
  - (A) ORGANISM: MURIDAE
  - (F) TISSUE TYPE: EMBRYO
- (ix) FEATURE:
  - (A) NAME/KEY: CDS
  - (B) LOCATION: 104..1393
  - (D) OTHER INFORMATION: /note= "MOP1 (CDNA)"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:

|                                                                   |     |
|-------------------------------------------------------------------|-----|
| CTGCAGCAAG TGACCTCGGG TCGTGGACCG CTGCCCTGCC CCCTCCGCTG CCACCTGGGG | 60  |
| CGGCGCGGGC CCGGTGCCCC GGATCGCGCG TAGAGCCGGC GCG ATG CAC GTG CGC   | 115 |
| Met His Val Arg                                                   |     |
| 1                                                                 |     |
| TCG CTG CGC GCT GCG GCG CCA CAC AGC TTC GTG GCG CTC TGG GCG CCT   | 163 |
| Ser Leu Arg Ala Ala Ala Pro His Ser Phe Val Ala Leu Trp Ala Pro   |     |
| 5 10 15 20                                                        |     |
| CTG TTC TTG CTG CGC TCC GCC CTG GCC GAT TTC AGC CTG GAC AAC GAG   | 211 |
| Leu Phe Leu Leu Arg Ser Ala Leu Ala Asp Phe Ser Leu Asp Asn Glu   |     |
| 25 30 35                                                          |     |
| GTG CAC TCC AGC TTC ATC CAC CGG CGC CTC CGC AGC CAG GAG CGG CGG   | 259 |
| Val His Ser Ser Phe Ile His Arg Arg Leu Arg Ser Gln Glu Arg Arg   |     |
| 40 45 50                                                          |     |
| GAG ATG CAG CGG GAG ATC CTG TCC ATC TTA GGG TTG CCC CAT CGC CCG   | 307 |
| Glu Met Gln Arg Glu Ile Leu Ser Ile Leu Gly Leu Pro His Arg Pro   |     |
| 55 60 65                                                          |     |
| CGC CCG CAC CTC CAG GGA AAG CAT AAT TCG GCG CCC ATG TTC ATG TTG   | 355 |
| Arg Pro His Leu Gln Gly Lys His Asn Ser Ala Pro Met Phe Met Leu   |     |
| 70 75 80                                                          |     |
| GAC CTG TAC AAC GCC ATG GCG GTG GAG GAG AGC GGG CCG GAC GGA CAG   | 403 |
| Asp Leu Tyr Asn Ala Met Ala Val Glu Glu Ser Gly Pro Asp Gly Gln   |     |
| 85 90 95 100                                                      |     |
| GGC TTC TCC TAC CCC TAC AAG GCC GTC TTC AGT ACC CAG GGC CCC CCT   | 451 |
| Gly Phe Ser Tyr Pro Tyr Lys Ala Val Phe Ser Thr Gln Gly Pro Pro   |     |
| 105 110 115                                                       |     |
| TTA GCC AGC CTG CAG GAC AGC CAT TTC CTC ACT GAC GCC GAC ATG GTC   | 499 |
| Leu Ala Ser Leu Gln Asp Ser His Phe Leu Thr Asp Ala Asp Met Val   |     |
| 120 125 130                                                       |     |
| ATG AGC TTC GTC AAC CTA GTG GAA CAT GAC AAA GAA TTC TTC CAC CCT   | 547 |
| Met Ser Phe Val Asn Leu Val Glu His Asp Lys Glu Phe Phe His Pro   |     |
| 135 140 145                                                       |     |
| CGA TAC CAC CAT CGG GAG TTC CGG TTT GAT CTT TCC AAG ATC CCC GAG   | 595 |
| Arg Tyr His His Arg Glu Phe Arg Phe Asp Leu Ser Lys Ile Pro Glu   |     |
| 150 155 160                                                       |     |
| GGC GAA CGG GTG ACC GCA GCC GAA TTC AGG ATC TAT AAG GAC TAC ATC   | 643 |
| Gly Glu Arg Val Thr Ala Ala Glu Phe Arg Ile Tyr Lys Asp Tyr Ile   |     |
| 165 170 175 180                                                   |     |
| CGG GAG CGA TTT GAC AAC GAG ACC TTC CAG ATC ACA GTC TAT CAG GTG   | 691 |
| Arg Glu Arg Phe Asp Asn Glu Thr Phe Gln Ile Thr Val Tyr Gln Val   |     |

|     |     |     |     | 185 |     |     |     | 190 |     |     |     | 195 |     |     |     |     |  |      |  |  |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|--|------|--|--|
| CTC | CAG | GAG | CAC | TCA | GGC | AGG | GAG | TCG | GAC | CTC | TTC | TTG | CTG | GAC | AGC |     |  | 739  |  |  |
| Leu | Gln | Glu | His | Ser | Gly | Arg | Glu | Ser | Asp | Leu | Phe | Leu | Leu | Asp | Ser |     |  |      |  |  |
| 200 |     |     |     |     |     |     |     | 205 |     |     |     | 210 |     |     |     |     |  |      |  |  |
| CGC | ACC | ATC | TGG | GCT | TCT | GAG | GAG | GGC | TGG | TTG | GTG | TTT | GAT | ATC | ACA |     |  | 787  |  |  |
| Arg | Thr | Ile | Trp | Ala | Ser | Glu | Glu | Gly | Trp | Leu | Val | Phe | Asp | Ile | Thr |     |  |      |  |  |
| 215 |     |     |     |     |     |     |     | 220 |     |     |     | 225 |     |     |     |     |  |      |  |  |
| GCC | ACC | AGC | AAC | CAC | TGG | GTG | GTC | AAC | CCT | CGG | CAC | AAC | CTG | GGC | TTA |     |  | 835  |  |  |
| Ala | Thr | Ser | Asn | His | Trp | Val | Val | Asn | Pro | Arg | His | Asn | Leu | Gly | Leu |     |  |      |  |  |
| 230 |     |     |     |     |     |     |     | 235 |     |     |     | 240 |     |     |     |     |  |      |  |  |
| CAG | CTC | TCT | GTG | GAG | ACC | CTG | GAT | GGG | CAG | AGC | ATC | AAC | CCC | AAG | TTG |     |  | 883  |  |  |
| Gln | Leu | Ser | Val | Glu | Thr | Leu | Asp | Gly | Gln | Ser | Ile | Asn | Pro | Lys | Leu |     |  |      |  |  |
| 245 |     |     |     |     |     |     |     | 250 |     |     |     | 255 |     |     |     | 260 |  |      |  |  |
| GCA | GGC | CTG | ATT | GGA | CGG | CAT | GGA | CCC | CAG | AAC | AAG | CAA | CCC | TTC | ATG |     |  | 931  |  |  |
| Ala | Gly | Leu | Ile | Gly | Arg | His | Gly | Pro | Gln | Asn | Lys | Gln | Pro | Phe | Met |     |  |      |  |  |
|     |     |     |     | 265 |     |     |     | 270 |     |     |     | 275 |     |     |     |     |  |      |  |  |
| GTG | GCC | TTC | TTC | AAG | GCC | ACG | GAA | GTC | CAT | CTC | CGT | AGT | ATC | CGG | TCC |     |  | 979  |  |  |
| Val | Ala | Phe | Phe | Lys | Ala | Thr | Glu | Val | His | Leu | Arg | Ser | Ile | Arg | Ser |     |  |      |  |  |
|     |     |     |     | 280 |     |     |     | 285 |     |     |     | 290 |     |     |     |     |  |      |  |  |
| ACG | GGG | GGC | AAG | CAG | CGC | AGC | CAG | AAT | CGC | TCC | AAG | ACG | CCA | AAG | AAC |     |  | 1027 |  |  |
| Thr | Gly | Gly | Lys | Gln | Arg | Ser | Gln | Asn | Arg | Ser | Lys | Thr | Pro | Lys | Asn |     |  |      |  |  |
| 295 |     |     |     |     |     |     |     | 300 |     |     |     | 305 |     |     |     |     |  |      |  |  |
| CAA | GAG | GCC | CTG | AGG | ATG | GCC | AGT | GTG | GCA | GAA | AAC | AGC | AGC | AGT | GAC |     |  | 1075 |  |  |
| Gln | Glu | Ala | Leu | Arg | Met | Ala | Ser | Val | Ala | Glu | Asn | Ser | Ser | Ser | Asp |     |  |      |  |  |
| 310 |     |     |     |     |     |     |     | 315 |     |     |     | 320 |     |     |     |     |  |      |  |  |
| CAG | AGG | CAG | GCC | TGC | AAG | AAA | CAT | GAG | CTG | TAC | GTC | AGC | TTC | CGA | GAC |     |  | 1123 |  |  |
| Gln | Arg | Gln | Ala | Cys | Lys | Lys | His | Glu | Leu | Tyr | Val | Ser | Phe | Arg | Asp |     |  |      |  |  |
| 325 |     |     |     |     |     |     |     | 330 |     |     |     | 335 |     |     |     | 340 |  |      |  |  |
| CTT | GGC | TGG | CAG | GAC | TGG | ATC | ATT | GCA | CCT | GAA | GGC | TAT | GCT | GCC | TAC |     |  | 1171 |  |  |
| Leu | Gly | Trp | Gln | Asp | Trp | Ile | Ile | Ala | Pro | Glu | Gly | Tyr | Ala | Ala | Tyr |     |  |      |  |  |
|     |     |     |     | 345 |     |     |     | 350 |     |     |     | 355 |     |     |     |     |  |      |  |  |
| TAC | TGT | GAG | GGA | GAG | TGC | GCC | TTC | CCT | CTG | AAC | TCC | TAC | ATG | AAC | GCC |     |  | 1219 |  |  |
| Tyr | Cys | Glu | Gly | Glu | Cys | Ala | Phe | Pro | Leu | Asn | Ser | Tyr | Met | Asn | Ala |     |  |      |  |  |
| 360 |     |     |     |     |     |     |     | 365 |     |     |     | 370 |     |     |     |     |  |      |  |  |
| ACC | AAC | CAC | GCC | ATC | GTC | CAG | ACA | CTG | GTT | CAC | TTC | ATC | AAC | CCA | GAC |     |  | 1267 |  |  |
| Thr | Asn | His | Ala | Ile | Val | Gln | Thr | Leu | Val | His | Phe | Ile | Asn | Pro | Asp |     |  |      |  |  |
| 375 |     |     |     |     |     |     |     | 380 |     |     |     | 385 |     |     |     |     |  |      |  |  |
| ACA | GTA | CCC | AAG | CCC | TGC | TGT | GCG | CCC | ACC | CAG | CTC | AAC | GCC | ATC | TCT |     |  | 1315 |  |  |
| Thr | Val | Pro | Lys | Pro | Cys | Cys | Ala | Pro | Thr | Gln | Leu | Asn | Ala | Ile | Ser |     |  |      |  |  |
| 390 |     |     |     |     |     |     |     | 395 |     |     |     | 400 |     |     |     |     |  |      |  |  |

GTC CTC TAC TTC GAC GAC AGC TCT AAT GTC ATC CTG AAG AAG TAC AGA 1363  
Val Leu Tyr Phe Asp Asp Ser Ser Asn Val Ile Leu Lys Lys Tyr Arg  
405 410 415 420

AAC ATG GTG GTC CGG GCC TGT GGC TGC CAC TAGCTCTTCC TGAGACCCTG 1413  
Asn Met Val Val Arg Ala Cys Gly Cys His  
425 430

ACCTTTGCGG GGCCACACCT TTCCAAATCT TCGATGTCTC ACCATCTAAG TCTCTCACTG 1473

CCCACCTTGG CGAGGAGAAC AGACCAACCT CTCCTGAGCC TTCCCTCACC TCCCAACCGG 1533

AAGCATGTAA GGGTTCCAGA AACCTGAGCG TGCAGCAGCT GATGAGCGCC CTTTCCTTCT 1593

GGCACGTGAC GGACAAGATC CTACCAGCTA CCACAGCAAA CGCCTAAGAG CAGGAAAAAT 1653

GTCTGCCAGG AAAGTGTCCA GTGTCCACAT GGCCCTGGC GCTCTGAGTC TTTGAGGAGT 1713

AATCGCAAGC CTCGTTGAGC TGCAGCAGAA GGAAGGGCTT AGCCAGGGTG GGCGCTGGCG 1773

TCTGTGTTGA AGGGAAACCA AGCAGAAGCC ACTGTAATGA TATGTCACAA TAAAACCCAT 1833

GAATGAAAAA AAAAAAAAAA AAAAAAAAAA AAAAGAATTC 1873

(2) INFORMATION FOR SEQ ID NO:19:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 430 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(ix) FEATURE:

- (D) OTHER INFORMATION: /product= "mOP1-PP"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:

Met His Val Arg Ser Leu Arg Ala Ala Ala Pro His Ser Phe Val Ala  
1 5 10 15

Leu Trp Ala Pro Leu Phe Leu Leu Arg Ser Ala Leu Ala Asp Phe Ser  
20 25 30

Leu Asp Asn Glu Val His Ser Ser Phe Ile His Arg Arg Leu Arg Ser  
35 40 45

Gln Glu Arg Arg Glu Met Gln Arg Glu Ile Leu Ser Ile Leu Gly Leu  
50 55 60

Pro His Arg Pro Arg Pro His Leu Gln Gly Lys His Asn Ser Ala Pro  
65 70 75 80

Met Phe Met Leu Asp Leu Tyr Asn Ala Met Ala Val Glu Glu Ser Gly  
85 90 95

Pro Asp Gly Gln Gly Phe Ser Tyr Pro Tyr Lys Ala Val Phe Ser Thr  
100 105 110

Gln Gly Pro Pro Leu Ala Ser Leu Gln Asp Ser His Phe Leu Thr Asp  
115 120 125

Ala Asp Met Val Met Ser Phe Val Asn Leu Val Glu His Asp Lys Glu  
130 135 140

Phe Phe His Pro Arg Tyr His His Arg Glu Phe Arg Phe Asp Leu Ser  
145 150 155 160

Lys Ile Pro Glu Gly Glu Arg Val Thr Ala Ala Glu Phe Arg Ile Tyr  
165 170 175

Lys Asp Tyr Ile Arg Glu Arg Phe Asp Asn Glu Thr Phe Gln Ile Thr  
180 185 190

Val Tyr Gln Val Leu Gln Glu His Ser Gly Arg Glu Ser Asp Leu Phe  
195 200 205

Leu Leu Asp Ser Arg Thr Ile Trp Ala Ser Glu Glu Gly Trp Leu Val  
210 215 220

Phe Asp Ile Thr Ala Thr Ser Asn His Trp Val Val Asn Pro Arg His  
225 230 235 240

Asn Leu Gly Leu Gln Leu Ser Val Glu Thr Leu Asp Gly Gln Ser Ile  
245 250 255

Asn Pro Lys Leu Ala Gly Leu Ile Gly Arg His Gly Pro Gln Asn Lys  
260 265 270

Gln Pro Phe Met Val Ala Phe Phe Lys Ala Thr Glu Val His Leu Arg  
275 280 285

Ser Ile Arg Ser Thr Gly Gly Lys Gln Arg Ser Gln Asn Arg Ser Lys  
290 295 300

Thr Pro Lys Asn Gln Glu Ala Leu Arg Met Ala Ser Val Ala Glu Asn  
305 310 315 320

Ser Ser Ser Asp Gln Arg Gln Ala Cys Lys Lys His Glu Leu Tyr Val  
325 330 335

Ser Phe Arg Asp Leu Gly Trp Gln Asp Trp Ile Ile Ala Pro Glu Gly  
340 345 350

Tyr Ala Ala Tyr Tyr Cys Glu Gly Glu Cys Ala Phe Pro Leu Asn Ser

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|--|
|     | 355 |     |     |     |     | 360 |     |     |     |     | 365 |     |     |     |     |  |
| Tyr | Met | Asn | Ala | Thr | Asn | His | Ala | Ile | Val | Gln | Thr | Leu | Val | His | Phe |  |
|     | 370 |     |     |     |     | 375 |     |     |     |     | 380 |     |     |     |     |  |
| Ile | Asn | Pro | Asp | Thr | Val | Pro | Lys | Pro | Cys | Cys | Ala | Pro | Thr | Gln | Leu |  |
| 385 |     |     |     |     | 390 |     |     |     |     | 395 |     |     |     | 400 |     |  |
| Asn | Ala | Ile | Ser | Val | Leu | Tyr | Phe | Asp | Asp | Ser | Ser | Asn | Val | Ile | Leu |  |
|     |     |     |     | 405 |     |     |     |     | 410 |     |     |     |     | 415 |     |  |
| Lys | Lys | Tyr | Arg | Asn | Met | Val | Val | Arg | Ala | Cys | Gly | Cys | His |     |     |  |
|     |     |     | 420 |     |     |     |     | 425 |     |     |     |     | 430 |     |     |  |

(2) INFORMATION FOR SEQ ID NO:20:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1723 base pairs  
(B) TYPE: nucleic acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(vi) ORIGINAL SOURCE:

- (A) ORGANISM: Homo sapiens  
(F) TISSUE TYPE: HIPPOCAMPUS

(ix) FEATURE:

- (A) NAME/KEY: CDS  
(B) LOCATION: 490..1696  
(D) OTHER INFORMATION: /note= "hOP2 (cDNA)"

(xi)SEQUENCE DESCRIPTION: SEQ ID NO:20:

|            |                                                     |            |            |            |             |     |
|------------|-----------------------------------------------------|------------|------------|------------|-------------|-----|
| GGCGCCGGCA | GAGCAGGAGT                                          | GGCTGGAGGA | GCTGTGGTTG | GAGCAGGAGG | TGGCACGGCA  | 60  |
| GGGCTGGAGG | GCTCCCTATG                                          | AGTGGCGGAG | ACGGCCCAGG | AGGCGCTGGA | GCAACAGCTC  | 120 |
| CCACACCGCA | CCAAGCGGTG                                          | GCTGCAGGAG | CTCGCCCATC | GCCCTGCGC  | TGCTCGGACC  | 180 |
| GCGGCCACAG | CCGGA CTGGC                                         | GGGTACGGCG | GCGACAGAGG | CATTGGCCGA | GAGTCCCAGT  | 240 |
| CCGCAGAGTA | GCCCCGGCCT                                          | CGAGGCGGTG | GCGTCCCGGT | CCTCTCCGTC | CAGGAGCCAG  | 300 |
| GACAGGTGTC | GCGCGGCGGG                                          | GCTCCAGGGA | CCGCGCCTGA | GGCCGGCTGC | CCGCCC GTCC | 360 |
| CGCCCCGCCC | CGCCGCCCGC                                          | CGCCCGCCGA | GCCCAGCCTC | CTTGCCGTG  | GGGCGTCCCC  | 420 |
| AGGCCCTGGG | TCGGCCGCGG                                          | AGCCGATGCG | CGCCCGCTGA | GCGCCCCAGC | TGAGCGCCCC  | 480 |
| CGGCCTGCC  | ATG ACC GCG CTC CCC GGC CCG CTC TGG CTC CTG GGC CTG |            |            |            |             | 528 |
|            | Met Thr Ala Leu Pro Gly Pro Leu Trp Leu Leu Gly Leu |            |            |            |             |     |

| 1                                                                                                                                                     | 5 | 10 |      |
|-------------------------------------------------------------------------------------------------------------------------------------------------------|---|----|------|
| GCG CTA TGC GCG CTG GGC GGG GGC GGC CCC GGC CTG CGA CCC CCG CCC<br>Ala Leu Cys Ala Leu Gly Gly Gly Gly Pro Gly Leu Arg Pro Pro Pro<br>15 20 25        |   |    | 576  |
| GGC TGT CCC CAG CGA CGT CTG GGC GCG CGC GAG CGC CGG GAC GTG CAG<br>Gly Cys Pro Gln Arg Arg Leu Gly Ala Arg Glu Arg Arg Asp Val Gln<br>30 35 40 45     |   |    | 624  |
| CGC GAG ATC CTG GCG GTG CTC GGG CTG CCT GGG CGG CCC CGG CCC CGC<br>Arg Glu Ile Leu Ala Val Leu Gly Leu Pro Gly Arg Pro Arg Pro Arg<br>50 55 60        |   |    | 672  |
| GCG CCA CCC GCC GCC TCC CGG CTG CCC GCG TCC GCG CCG CTC TTC ATG<br>Ala Pro Pro Ala Ala Ser Arg Leu Pro Ala Ser Ala Pro Leu Phe Met<br>65 70 75        |   |    | 720  |
| CTG GAC CTG TAC CAC GCC ATG GCC GGC GAC GAC GAC GAG GAC GGC GCG<br>Leu Asp Leu Tyr His Ala Met Ala Gly Asp Asp Asp Glu Asp Gly Ala<br>80 85 90        |   |    | 768  |
| CCC GCG GAG CGG CGC CTG GGC CGC GCC GAC CTG GTC ATG AGC TTC GTT<br>Pro Ala Glu Arg Arg Leu Gly Arg Ala Asp Leu Val Met Ser Phe Val<br>95 100 105      |   |    | 816  |
| AAC ATG GTG GAG CGA GAC CGT GCC CTG GGC CAC CAG GAG CCC CAT TGG<br>Asn Met Val Glu Arg Asp Arg Ala Leu Gly His Gln Glu Pro His Trp<br>110 115 120 125 |   |    | 864  |
| AAG GAG TTC CGC TTT GAC CTG ACC CAG ATC CCG GCT GGG GAG GCG GTC<br>Lys Glu Phe Arg Phe Asp Leu Thr Gln Ile Pro Ala Gly Glu Ala Val<br>130 135 140     |   |    | 912  |
| ACA GCT GCG GAG TTC CGG ATT TAC AAG GTG CCC AGC ATC CAC CTG CTC<br>Thr Ala Ala Glu Phe Arg Ile Tyr Lys Val Pro Ser Ile His Leu Leu<br>145 150 155     |   |    | 960  |
| AAC AGG ACC CTC CAC GTC AGC ATG TTC CAG GTG GTC CAG GAG CAG TCC<br>Asn Arg Thr Leu His Val Ser Met Phe Gln Val Val Gln Glu Gln Ser<br>160 165 170     |   |    | 1008 |
| AAC AGG GAG TCT GAC TTG TTC TTT TTG GAT CTT CAG ACG CTC CGA GCT<br>Asn Arg Glu Ser Asp Leu Phe Phe Leu Asp Leu Gln Thr Leu Arg Ala<br>175 180 185     |   |    | 1056 |
| GGA GAC GAG GGC TGG CTG GTG CTG GAT GTC ACA GCA GCC AGT GAC TGC<br>Gly Asp Glu Gly Trp Leu Val Leu Asp Val Thr Ala Ala Ser Asp Cys<br>190 195 200 205 |   |    | 1104 |
| TGG TTG CTG AAG CGT CAC AAG GAC CTG GGA CTC CGC CTC TAT GTG GAG<br>Trp Leu Leu Lys Arg His Lys Asp Leu Gly Leu Arg Leu Tyr Val Glu<br>210 215 220     |   |    | 1152 |

|                                                                                                                                                       |      |
|-------------------------------------------------------------------------------------------------------------------------------------------------------|------|
| ACT GAG GAC GGG CAC AGC GTG GAT CCT GGC CTG GCC GGC CTG CTG GGT<br>Thr Glu Asp Gly His Ser Val Asp Pro Gly Leu Ala Gly Leu Leu Gly<br>225 230 235     | 1200 |
| CAA CGG GCC CCA CGC TCC CAA CAG CCT TTC GTG GTC ACT TTC TTC AGG<br>Gln Arg Ala Pro Arg Ser Gln Gln Pro Phe Val Val Thr Phe Phe Arg<br>240 245 250     | 1248 |
| GCC AGT CCG AGT CCC ATC CGC ACC CCT CGG GCA GTG AGG CCA CTG AGG<br>Ala Ser Pro Ser Pro Ile Arg Thr Pro Arg Ala Val Arg Pro Leu Arg<br>255 260 265     | 1296 |
| AGG AGG CAG CCG AAG AAA AGC AAC GAG CTG CCG CAG GCC AAC CGA CTC<br>Arg Arg Gln Pro Lys Lys Ser Asn Glu Leu Pro Gln Ala Asn Arg Leu<br>270 275 280 285 | 1344 |
| CCA GGG ATC TTT GAT GAC GTC CAC GGC TCC CAC GGC CGG CAG GTC TGC<br>Pro Gly Ile Phe Asp Asp Val His Gly Ser His Gly Arg Gln Val Cys<br>290 295 300     | 1392 |
| CGT CGG CAC GAG CTC TAC GTC AGC TTC CAG GAC CTC GGC TGG CTG GAC<br>Arg Arg His Glu Leu Tyr Val Ser Phe Gln Asp Leu Gly Trp Leu Asp<br>305 310 315     | 1440 |
| TGG GTC ATC GCT CCC CAA GGC TAC TCG GCC TAT TAC TGT GAG GGG GAG<br>Trp Val Ile Ala Pro Gln Gly Tyr Ser Ala Tyr Tyr Cys Glu Gly Glu<br>320 325 330     | 1488 |
| TGC TCC TTC CCA CTG GAC TCC TGC ATG AAT GCC ACC AAC CAC GCC ATC<br>Cys Ser Phe Pro Leu Asp Ser Cys Met Asn Ala Thr Asn His Ala Ile<br>335 340 345     | 1536 |
| CTG CAG TCC CTG GTG CAC CTG ATG AAG CCA AAC GCA GTC CCC AAG GCG<br>Leu Gln Ser Leu Val His Leu Met Lys Pro Asn Ala Val Pro Lys Ala<br>350 355 360 365 | 1584 |
| TGC TGT GCA CCC ACC AAG CTG AGC GCC ACC TCT GTG CTC TAC TAT GAC<br>Cys Cys Ala Pro Thr Lys Leu Ser Ala Thr Ser Val Leu Tyr Tyr Asp<br>370 375 380     | 1632 |
| AGC AGC AAC AAC GTC ATC CTG CGC AAA CAC CGC AAC ATG GTG GTC AAG<br>Ser Ser Asn Asn Val Ile Leu Arg Lys His Arg Asn Met Val Val Lys<br>385 390 395     | 1680 |
| GCC TGC GGC TGC CAC T CAGTCAGCCC GCCCAGCCCT ACTGCAG<br>Ala Cys Gly Cys His<br>400                                                                     | 1723 |

(2) INFORMATION FOR SEQ ID NO:21:

(i)SEQUENCE CHARACTERISTICS:

(A) LENGTH: 402 amino acids



(B) TYPE: amino acid

(D) TOPOLOGY: linear

(ii)MOLECULE TYPE: protein

(ix)FEATURE:

(A)OTHER INFORMATION: /product= "hOP2-PP"

(xi)SEQUENCE DESCRIPTION: SEQ ID NO:21:

Met Thr Ala Leu Pro Gly Pro Leu Trp Leu Leu Gly Leu Ala Leu Cys  
1 5 10 15  
Ala Leu Gly Gly Gly Gly Pro Gly Leu Arg Pro Pro Pro Gly Cys Pro  
20 25 30  
Gln Arg Arg Leu Gly Ala Arg Glu Arg Arg Asp Val Gln Arg Glu Ile  
35 40 45  
Leu Ala Val Leu Gly Leu Pro Gly Arg Pro Arg Pro Arg Ala Pro Pro  
50 55 60  
Ala Ala Ser Arg Leu Pro Ala Ser Ala Pro Leu Phe Met Leu Asp Leu  
65 70 75 80  
Tyr His Ala Met Ala Gly Asp Asp Asp Glu Asp Gly Ala Pro Ala Glu  
85 90 95  
Arg Arg Leu Gly Arg Ala Asp Leu Val Met Ser Phe Val Asn Met Val  
100 105 110  
Glu Arg Asp Arg Ala Leu Gly His Gln Glu Pro His Trp Lys Glu Phe  
115 120 125  
Arg Phe Asp Leu Thr Gln Ile Pro Ala Gly Glu Ala Val Thr Ala Ala  
130 135 140  
Glu Phe Arg Ile Tyr Lys Val Pro Ser Ile His Leu Leu Asn Arg Thr  
145 150 155 160  
Leu His Val Ser Met Phe Gln Val Val Gln Glu Gln Ser Asn Arg Glu  
165 170 175  
Ser Asp Leu Phe Phe Leu Asp Leu Gln Thr Leu Arg Ala Gly Asp Glu  
180 185 190  
Gly Trp Leu Val Leu Asp Val Thr Ala Ala Ser Asp Cys Trp Leu Leu  
195 200 205  
Lys Arg His Lys Asp Leu Gly Leu Arg Leu Tyr Val Glu Thr Glu Asp  
210 215 220  
Gly His Ser Val Asp Pro Gly Leu Ala Gly Leu Leu Gly Gln Arg Ala

225                      230                      235                      240

Pro Arg Ser Gln Gln Pro Phe Val Val Thr Phe Phe Arg Ala Ser Pro  
                                 245                      250                      255

Ser Pro Ile Arg Thr Pro Arg Ala Val Arg Pro Leu Arg Arg Arg Gln  
                                 260                      265                      270

Pro Lys Lys Ser Asn Glu Leu Pro Gln Ala Asn Arg Leu Pro Gly Ile  
                                 275                      280                      285

Phe Asp Asp Val His Gly Ser His Gly Arg Gln Val Cys Arg Arg His  
                                 290                      295                      300

Glu Leu Tyr Val Ser Phe Gln Asp Leu Gly Trp Leu Asp Trp Val Ile  
305                                   310                      315                      320

Ala Pro Gln Gly Tyr Ser Ala Tyr Tyr Cys Glu Gly Glu Cys Ser Phe  
                                 325                      330                      335

Pro Leu Asp Ser Cys Met Asn Ala Thr Asn His Ala Ile Leu Gln Ser  
                                 340                      345                      350

Leu Val His Leu Met Lys Pro Asn Ala Val Pro Lys Ala Cys Cys Ala  
                                 355                      360                      365

Pro Thr Lys Leu Ser Ala Thr Ser Val Leu Tyr Tyr Asp Ser Ser Asn  
370                                   375                      380

Asn Val Ile Leu Arg Lys His Arg Asn Met Val Val Lys Ala Cys Gly  
385                                   390                      395                      400

Cys His

(2) INFORMATION FOR SEQ ID NO:22:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 1926 base pairs
  - (B) TYPE: nucleic acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: cDNA
- (vi) ORIGINAL SOURCE:
  - (A) ORGANISM: MURIDAE
  - (F) TISSUE TYPE: EMBRYO
- (ix) FEATURE:
  - (A) NAME/KEY: CDS
  - (B) LOCATION: 93..1289
  - (D) OTHER INFORMATION: /note= "mOP2 cDNA"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:

|                                                                 |     |
|-----------------------------------------------------------------|-----|
| GCCAGGCACA GGTGCGCCGT CTGGTCCTCC CCGTCTGGCG TCAGCCGAGC          | 50  |
| CCGACCAGCT ACCAGTGGAT GCGCGCCGGC TGAAAGTCCG AG ATG GCT ATG CGT  | 104 |
| Met Ala Met Arg                                                 |     |
| 1                                                               |     |
| CCC GGG CCA CTC TGG CTA TTG GGC CTT GCT CTG TGC GCG CTG GGA GGC | 152 |
| Pro Gly Pro Leu Trp Leu Leu Gly Leu Ala Leu Cys Ala Leu Gly Gly |     |
| 5 10 15 20                                                      |     |
| GGC CAC GGT CCG CGT CCC CCG CAC ACC TGT CCC CAG CGT CGC CTG GGA | 200 |
| Gly His Gly Pro Arg Pro Pro His Thr Cys Pro Gln Arg Arg Leu Gly |     |
| 25 30 35                                                        |     |
| GCG CGC GAG CGC CGC GAC ATG CAG CGT GAA ATC CTG GCG GTG CTC GGG | 248 |
| Ala Arg Glu Arg Arg Asp Met Gln Arg Glu Ile Leu Ala Val Leu Gly |     |
| 40 45 50                                                        |     |
| CTA CCG GGA CGG CCC CGA CCC CGT GCA CAA CCC GCG GCT GCC CGG CAG | 296 |
| Leu Pro Gly Arg Pro Arg Pro Arg Ala Gln Pro Ala Ala Arg Gln     |     |
| 55 60 65                                                        |     |
| CCA GCG TCC GCG CCC CTC TTC ATG TTG GAC CTA TAC CAC GCC ATG ACC | 344 |
| Pro Ala Ser Ala Pro Leu Phe Met Leu Asp Leu Tyr His Ala Met Thr |     |
| 70 75 80                                                        |     |
| GAT GAC GAC GAC GGC GGG CCA CCA CAG GCT CAC TTA GGC CGT GCC GAC | 392 |
| Asp Asp Asp Asp Gly Gly Pro Pro Gln Ala His Leu Gly Arg Ala Asp |     |
| 85 90 95 100                                                    |     |
| CTG GTC ATG AGC TTC GTC AAC ATG GTG GAA CGC GAC CGT ACC CTG GGC | 440 |
| Leu Val Met Ser Phe Val Asn Met Val Glu Arg Asp Arg Thr Leu Gly |     |
| 105 110 115                                                     |     |
| TAC CAG GAG CCA CAC TGG AAG GAA TTC CAC TTT GAC CTA ACC CAG ATC | 488 |
| Tyr Gln Glu Pro His Trp Lys Glu Phe His Phe Asp Leu Thr Gln Ile |     |
| 120 125 130                                                     |     |
| CCT GCT GGG GAG GCT GTC ACA GCT GCT GAG TTC CGG ATC TAC AAA GAA | 536 |
| Pro Ala Gly Glu Ala Val Thr Ala Ala Glu Phe Arg Ile Tyr Lys Glu |     |
| 135 140 145                                                     |     |
| CCC AGC ACC CAC CCG CTC AAC ACA ACC CTC CAC ATC AGC ATG TTC GAA | 584 |
| Pro Ser Thr His Pro Leu Asn Thr Thr Leu His Ile Ser Met Phe Glu |     |
| 150 155 160                                                     |     |
| GTG GTC CAA GAG CAC TCC AAC AGG GAG TCT GAC TTG TTC TTT TTG GAT | 632 |
| Val Val Gln Glu His Ser Asn Arg Glu Ser Asp Leu Phe Phe Leu Asp |     |
| 165 170 175 180                                                 |     |
| CTT CAG ACG CTC CGA TCT GGG GAC GAG GGC TGG CTG GTG CTG GAC ATC | 680 |

|                                                                  |      |
|------------------------------------------------------------------|------|
| Leu Gln Thr Leu Arg Ser Gly Asp Glu Gly Trp Leu Val Leu Asp Ile  |      |
| 185 190 195                                                      |      |
| ACA GCA GCC AGT GAC CGA TGG CTG CTG AAC CAT CAC AAG GAC CTG GGA  | 728  |
| Thr Ala Ala Ser Asp Arg Trp Leu Leu Asn His His Lys Asp Leu Gly  |      |
| 200 205 210                                                      |      |
| CTC CGC CTC TAT GTG GAA ACC GCG GAT GGG CAC AGC ATG GAT CCT GGC  | 776  |
| Leu Arg Leu Tyr Val Glu Thr Ala Asp Gly His Ser Met Asp Pro Gly  |      |
| 215 220 225                                                      |      |
| CTG GCT GGT CTG CTT GGA CGA CAA GCA CCA CGC TCC AGA CAG CCT TTC  | 824  |
| Leu Ala Gly Leu Leu Gly Arg Gln Ala Pro Arg Ser Arg Gln Pro Phe  |      |
| 230 235 240                                                      |      |
| ATG GTA ACC TTC TTC AGG GCC AGC CAG AGT CCT GTG CGG GCC CCT CGG  | 872  |
| Met Val Thr Phe Phe Arg Ala Ser Gln Ser Pro Val Arg Ala Pro Arg  |      |
| 245 250 255 260                                                  |      |
| GCA GCG AGA CCA CTG AAG AGG AGG CAG CCA AAG AAA ACG AAC GAG CTT  | 920  |
| Ala Ala Arg Pro Leu Lys Arg Arg Gln Pro Lys Lys Thr Asn Glu Leu  |      |
| 265 270 275                                                      |      |
| CCG CAC CCC AAC AAA CTC CCA GGG ATC TTT GAT GAT GGC CAC GGT TCC  | 968  |
| Pro His Pro Asn Lys Leu Pro Gly Ile Phe Asp Asp Gly His Gly Ser  |      |
| 280 285 290                                                      |      |
| CGC GGC AGA GAG GTT TGC CGC AGG CAT GAG CTC TAC GTC AGC TTC CGT  | 1016 |
| Arg Gly Arg Glu Val Cys Arg Arg His Glu Leu Tyr Val Ser Phe Arg  |      |
| 295 300 305                                                      |      |
| GAC CTT GGC TGG CTG GAC TGG GTC ATC GCC CCC CAG GGC TAC TCT GCC  | 1064 |
| Asp Leu Gly Trp Leu Asp Trp Val Ile Ala Pro Gln Gly Tyr Ser Ala  |      |
| 310 315 320                                                      |      |
| TAT TAC TGT GAG GGG GAG TGT GCT TTC CCA CTG GAC TCC TGT ATG AAC  | 1112 |
| Tyr Tyr Cys Glu Gly Glu Cys Ala Phe Pro Leu Asp Ser Cys Met Asn  |      |
| 325 330 335 340                                                  |      |
| GCC ACC AAC CAT GCC ATC TTG CAG TCT CTG GTG CAC CTG ATG AAG CCA  | 1160 |
| Ala Thr Asn His Ala Ile Leu Gln Ser Leu Val His Leu Met Lys Pro  |      |
| 345 350 355                                                      |      |
| GAT GTT GTC CCC AAG GCA TGC TGT GCA CCC ACC AAA CTG AGT GCC ACC  | 1208 |
| Asp Val Val Pro Lys Ala Cys Cys Ala Pro Thr Lys Leu Ser Ala Thr  |      |
| 360 365 370                                                      |      |
| TCT GTG CTG TAC TAT GAC AGC AGC AAC AAT GTC ATC CTG CGT AAA CAC  | 1256 |
| Ser Val Leu Tyr Tyr Asp Ser Ser Asn Asn Val Ile Leu Arg Lys His  |      |
| 375 380 385                                                      |      |
| CGT AAC ATG GTG GTC AAG GCC TGT GGC TGC CAC TGAGGCCCG CCCAGCATCC | 1309 |
| Arg Asn Met Val Val Lys Ala Cys Gly Cys His                      |      |

390

395

TGCTTCTACT ACCTTACCAT CTGGCCGGGC CCCTCTCCAG AGGCAGAAAC CCTTCTATGT 1369  
TATCATAGCT CAGACAGGGG CAATGGGAGG CCCTTCACTT CCCCTGGCCA CTTCTGCTA 1429  
AAATTCTGGT CTTTCCCAGT TCCTCTGTCC TTCATGGGGT TTCGGGGCTA TCACCCCGCC 1489  
CTCTCCATCC TCCTACCCCA AGCATAGACT GAATGCACAC AGCATCCCAG AGCTATGCTA 1549  
ACTGAGAGGT CTGGGGTCAG CACTGAAGGC CCACATGAGG AAGACTGATC CTTGGCCATC 1609  
CTCAGCCCAC AATGGCAAAT TCTGGATGGT CTAAGAAGGC CGTGGAATTC TAAACTAGAT 1669  
GATCTGGGCT CTCTGCACCA TTCATTGTGG CAGTTGGGAC ATTTTtaggt ATAACAGACA 1729  
CATACTTA GATCAATGCA TCGCTGTACT CCTTGAAATC AGAGCTAGCT TGTTAGAAAA 1789  
AGAATCAGAG CCAGGTATAG CGGTGCATGT CATTAATCCC AGCGCTAAAG AGACAGAGAC 1849  
AGGAGAATCT CTGTGAGTTC AAGGCCACAT AGAAAGAGCC TGTCTCGGGA GCAGGAAAAA 1909  
AAAAAAAAAC GGAATTC 1926

(2) INFORMATION FOR SEQ ID NO:23:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 399 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(ix) FEATURE:

- (D) OTHER INFORMATION: /product= "mOP2-PP"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:

Met Ala Met Arg Pro Gly Pro Leu Trp Leu Leu Gly Leu Ala Leu Cys  
1 5 10 15  
Ala Leu Gly Gly Gly His Gly Pro Arg Pro Pro His Thr Cys Pro Gln  
20 25 30  
Arg Arg Leu Gly Ala Arg Glu Arg Arg Asp Met Gln Arg Glu Ile Leu Ala  
35 40 45  
Val Leu Gly Leu Pro Gly Arg Pro Arg Pro Arg Ala Gln Pro Ala Ala  
50 55 60 65  
Ala Arg Gln Pro Ala Ser Ala Pro Leu Phe Met Leu Asp Leu Tyr His Ala  
70 75 80

Met Thr Asp Asp Asp Asp Gly Gly Pro Pro Gln Ala His Leu Gly Arg  
85 90 95

Ala Asp Leu Val Met Ser Phe Val Asn Met Val Glu Arg Asp Arg Thr  
100 105 110

Leu Gly Tyr Gln Glu Pro His Trp Lys Glu Phe His Phe Asp Leu Thr  
115 120 125 130

Gln Ile Pro Ala Gly Glu Ala Val Thr Ala Ala Glu Phe Arg Ile Tyr  
135 140 145

Lys Glu Pro Ser Thr His Pro Leu Asn Thr Thr Leu His Ile Ser Met  
150 155 160

Phe Glu Val Val Gln Glu His Ser Asn Arg Glu Ser Asp Leu Phe Phe  
165 170 175

Leu Asp Leu Gln Thr Leu Arg Ser Gly Asp Glu Gly Trp Leu Val Leu  
180 185 190

Asp Ile Thr Ala Ala Ser Asp Arg Trp Leu Leu Asn His His Lys Asp  
195 200 205 210

Leu Gly Leu Arg Leu Tyr Val Glu Thr Ala Asp Gly His Ser Met Asp  
215 220 225

Pro Gly Leu Ala Gly Leu Leu Gly Arg Gln Ala Pro Arg Ser Arg Gln  
230 235 240

Pro Phe Met Val Thr Phe Phe Arg Ala Ser Gln Ser Pro Val Arg Ala  
245 250 255

Pro Arg Ala Ala Arg Pro Leu Lys Arg Arg Gln Pro Lys Lys Thr Asn  
260 265 270

Glu Leu Pro His Pro Asn Lys Leu Pro Gly Ile Phe Asp Asp Gly His  
275 280 285 290

Gly Ser Arg Gly Arg Glu Val Cys Arg Arg His Glu Leu Tyr Val Ser  
295 300 305

Phe Arg Asp Leu Gly Trp Leu Asp Trp Val Ile Ala Pro Gln Gly Tyr  
310 315 320

Ser Ala Tyr Tyr Cys Glu Gly Glu Cys Ala Phe Pro Leu Asp Ser Cys  
325 330 335

Met Asn Ala Thr Asn His Ala Ile Leu Gln Ser Leu Val His Leu Met  
340 345 350

Lys Pro Asp Val Val Pro Lys Ala Cys Cys Ala Pro Thr Lys Leu Ser  
355 360 365 370

Ala Thr Ser Val Leu Tyr Tyr Asp Ser Ser Asn Asn Val Ile Leu Arg  
375 380 385

Lys His Arg Asn Met Val Val Lys Ala Cys Gly Cys His  
390 395

(2) INFORMATION FOR SEQ ID NO:24:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1368 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:

- (A) NAME/KEY: CDS
- (B) LOCATION: 1..1368
- (D) OTHER INFORMATION: /STANDARD NAME="60A"

(x) PUBLICATION INFORMATION:

- (A) AUTHORS: WHARTON, KRISTI A.; THOMSEN, GERALD H.; GELBERT, WILLIAM M.
- (B) TITLE: DROSOPHILA 60A GENE...
- (C) JOURNAL: PROC. NAT'L ACAD. SCI. USA
- (D) VOLUME: 88
- (E) RELEVANT RESIDUES IN SEQ ID NO:3: FROM 1 TO 1368
- (F) PAGES: 9214-9218
- (G) DATE: OCT - 1991

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:

|                                                                 |     |
|-----------------------------------------------------------------|-----|
| ATG TCG GGA CTG CGA AAC ACC TCG GAG GCC GTT GCA GTG CTC GCC TCC | 48  |
| Met Ser Gly Leu Arg Asn Thr Ser Glu Ala Val Ala Val Leu Ala Ser |     |
| 1 5 10 15                                                       |     |
| CTG GGA CTC GGA ATG GTT CTG CTC ATG TTC GTG GCG ACC ACG CCG CCG | 96  |
| Leu Gly Leu Gly Met Val Leu Leu Met Phe Val Ala Thr Thr Pro Pro |     |
| 20 25 30                                                        |     |
| GCC GTT GAG GCC ACC CAG TCG GGG ATT TAC ATA GAC AAC GGC AAG GAC | 144 |
| Ala Val Glu Ala Thr Gln Ser Gly Ile Tyr Ile Asp Asn Gly Lys Asp |     |
| 35 40 45                                                        |     |
| CAG ACG ATC ATG CAC AGA GTG CTG AGC GAG GAC GAC AAG CTG GAC GTC | 192 |
| Gln Thr Ile Met His Arg Val Leu Ser Glu Asp Asp Lys Leu Asp Val |     |
| 50 55 60                                                        |     |
| TCG TAC GAG ATC CTC GAG TTC CTG GGC ATC GCC GAA CGG CCG ACG CAC | 240 |
| Ser Tyr Glu Ile Leu Glu Phe Leu Gly Ile Ala Glu Arg Pro Thr His |     |
| 65 70 75 80                                                     |     |

000290" 4546560

|                                                                                                                                                       |     |
|-------------------------------------------------------------------------------------------------------------------------------------------------------|-----|
| CTG AGC AGC CAC CAG TTG TCG CTG AGG AAG TCG GCT CCC AAG TTC CTG<br>Leu Ser Ser His Gln Leu Ser Leu Arg Lys Ser Ala Pro Lys Phe Leu<br>85 90 95        | 288 |
| CTG GAC GTC TAC CAC CGC ATC ACG GCG GAG GAG GGT CTC AGC GAT CAG<br>Leu Asp Val Tyr His Arg Ile Thr Ala Glu Glu Gly Leu Ser Asp Gln<br>100 105 110     | 336 |
| GAT GAG GAC GAC GAC TAC GAA CGC GGC CAT CGG TCC AGG AGG AGC GCC<br>Asp Glu Asp Asp Asp Tyr Glu Arg Gly His Arg Ser Arg Arg Ser Ala<br>115 120 125     | 384 |
| GAC CTC GAG GAG GAT GAG GGC GAG CAG CAG AAG AAC TTC ATC ACC GAC<br>Asp Leu Glu Glu Asp Glu Gly Glu Gln Gln Lys Asn Phe Ile Thr Asp<br>130 135 140     | 432 |
| CTG GAC AAG CGG GCC ATC GAC GAG AGC GAC ATC ATC ATG ACC TTC CTG<br>Leu Asp Lys Arg Ala Ile Asp Glu Ser Asp Ile Ile Met Thr Phe Leu<br>145 150 155 160 | 480 |
| AAC AAG CGC CAC CAC AAT GTG GAC GAA CTG CGT CAC GAG CAC GGC CGT<br>Asn Lys Arg His His Asn Val Asp Glu Leu Arg His Glu His Gly Arg<br>165 170 175     | 528 |
| CGC CTG TGG TTC GAC GTC TCC AAC GTG CCC AAC GAC AAC TAC CTG GTG<br>Arg Leu Trp Phe Asp Val Ser Asn Val Pro Asn Asp Asn Tyr Leu Val<br>180 185 190     | 576 |
| ATG GCC GAG CTG CGC ATC TAT CAG AAC GCC AAC GAG GGC AAG TGG CTG<br>Met Ala Glu Leu Arg Ile Tyr Gln Asn Ala Asn Glu Gly Lys Trp Leu<br>195 200 205     | 624 |
| ACC GCC AAC AGG GAG TTC ACC ATC ACG GTA TAC GCC ATT GGC ACC GGC<br>Thr Ala Asn Arg Glu Phe Thr Ile Thr Val Tyr Ala Ile Gly Thr Gly<br>210 215 220     | 672 |
| ACG CTG GGC CAG CAC ACC ATG GAG CCG CTG TCC TCG GTG AAC ACC ACC<br>Thr Leu Gly Gln His Thr Met Glu Pro Leu Ser Ser Val Asn Thr Thr<br>225 230 235 240 | 720 |
| GGG GAC TAC GTG GGC TGG TTG GAG CTC AAC GTG ACC GAG GGC CTG CAC<br>Gly Asp Tyr Val Gly Trp Leu Glu Leu Asn Val Thr Glu Gly Leu His<br>245 250 255     | 768 |
| GAG TGG CTG GTC AAG TCG AAG GAC AAT CAT GGC ATC TAC ATT GGA GCA<br>Glu Trp Leu Val Lys Ser Lys Asp Asn His Gly Ile Tyr Ile Gly Ala<br>260 265 270     | 816 |
| CAC GCT GTC AAC CGA CCC GAC CGC GAG GTG AAG CTG GAC GAC ATT GGA<br>His Ala Val Asn Arg Pro Asp Arg Glu Val Lys Leu Asp Asp Ile Gly<br>275 280 285     | 864 |



|                                                                                                                                                       |      |
|-------------------------------------------------------------------------------------------------------------------------------------------------------|------|
| CTG ATC CAC CGC AAG GTG GAC GAC GAG TTC CAG CCC TTC ATG ATC GGC<br>Leu Ile His Arg Lys Val Asp Asp Glu Phe Gln Pro Phe Met Ile Gly<br>290 295 300     | 912  |
| TTC TTC CGC GGA CCG GAG CTG ATC AAG GCG ACG GCC CAC AGC AGC CAC<br>Phe Phe Arg Gly Pro Glu Leu Ile Lys Ala Thr Ala His Ser Ser His<br>305 310 315 320 | 960  |
| CAC AGG AGC AAG CGA AGC GCC AGC CAT CCA CGC AAG CGC AAG AAG TCG<br>His Arg Ser Lys Arg Ser Ala Ser His Pro Arg Lys Arg Lys Lys Ser<br>325 330 335     | 1008 |
| GTG TCG CCC AAC AAC GTG CCG CTG CTG GAA CCG ATG GAG AGC ACG CGC<br>Val Ser Pro Asn Asn Val Pro Leu Leu Glu Pro Met Glu Ser Thr Arg<br>340 345 350     | 1056 |
| AGC TGC CAG ATG CAG ACC CTG TAC ATA GAC TTC AAG GAT CTG GGC TGG<br>Ser Cys Gln Met Gln Thr Leu Tyr Ile Asp Phe Lys Asp Leu Gly Trp<br>355 360 365     | 1104 |
| CAT GAC TGG ATC ATC GCA CCA GAG GGC TAT GGC GCC TTC TAC TGC AGC<br>His Asp Trp Ile Ile Ala Pro Glu Gly Tyr Gly Ala Phe Tyr Cys Ser<br>370 375 380     | 1152 |
| GGC GAG TGC AAT TTC CCG CTC AAT GCG CAC ATG AAC GCC ACG AAC CAT<br>Gly Glu Cys Asn Phe Pro Leu Asn Ala His Met Asn Ala Thr Asn His<br>385 390 395 400 | 1200 |
| GCG ATC GTC CAG ACC CTG GTC CAC CTG CTG GAG CCC AAG AAG GTG CCC<br>Ala Ile Val Gln Thr Leu Val His Leu Leu Glu Pro Lys Lys Val Pro<br>405 410 415     | 1248 |
| AAG CCC TGC TGC GCT CCG ACC AGG CTG GGA GCA CTA CCC GTT CTG TAC<br>Lys Pro Cys Cys Ala Pro Thr Arg Leu Gly Ala Leu Pro Val Leu Tyr<br>420 425 430     | 1296 |
| CAC CTG AAC GAC GAG AAT GTG AAC CTG AAA AAG TAT AGA AAC ATG ATT<br>His Leu Asn Asp Glu Asn Val Asn Leu Lys Lys Tyr Arg Asn Met Ile<br>435 440 445     | 1344 |
| GTG AAA TCC TGC GGG TGC CAT TGA<br>Val Lys Ser Cys Gly Cys His<br>450 455                                                                             | 1368 |

(2) INFORMATION FOR SEQ ID NO:25:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 455 amino acids
  - (B) TYPE: amino acid
  - (D) TOPOLOGY: linear

- (ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:25:

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Met | Ser | Gly | Leu | Arg | Asn | Thr | Ser | Glu | Ala | Val | Ala | Val | Leu | Ala | Ser | 1   | 5   | 10  | 15  |
| Leu | Gly | Leu | Gly | Met | Val | Leu | Leu | Met | Phe | Val | Ala | Thr | Thr | Pro | Pro | 20  | 25  | 30  |     |
| Ala | Val | Glu | Ala | Thr | Gln | Ser | Gly | Ile | Tyr | Ile | Asp | Asn | Gly | Lys | Asp | 35  | 40  | 45  |     |
| Gln | Thr | Ile | Met | His | Arg | Val | Leu | Ser | Glu | Asp | Asp | Lys | Leu | Asp | Val | 50  | 55  | 60  |     |
| Ser | Tyr | Glu | Ile | Leu | Glu | Phe | Leu | Gly | Ile | Ala | Glu | Arg | Pro | Thr | His | 65  | 70  | 75  | 80  |
| Leu | Ser | Ser | His | Gln | Leu | Ser | Leu | Arg | Lys | Ser | Ala | Pro | Lys | Phe | Leu | 85  | 90  | 95  |     |
| Leu | Asp | Val | Tyr | His | Arg | Ile | Thr | Ala | Glu | Glu | Gly | Leu | Ser | Asp | Gln | 100 | 105 | 110 |     |
| Asp | Glu | Asp | Asp | Asp | Tyr | Glu | Arg | Gly | His | Arg | Ser | Arg | Arg | Ser | Ala | 115 | 120 | 125 |     |
| Asp | Leu | Glu | Glu | Asp | Glu | Gly | Glu | Gln | Gln | Lys | Asn | Phe | Ile | Thr | Asp | 130 | 135 | 140 |     |
| Leu | Asp | Lys | Arg | Ala | Ile | Asp | Glu | Ser | Asp | Ile | Ile | Met | Thr | Phe | Leu | 145 | 150 | 155 | 160 |
| Asn | Lys | Arg | His | His | Asn | Val | Asp | Glu | Leu | Arg | His | Glu | His | Gly | Arg | 165 | 170 | 175 |     |
| Arg | Leu | Trp | Phe | Asp | Val | Ser | Asn | Val | Pro | Asn | Asp | Asn | Tyr | Leu | Val | 180 | 185 | 190 |     |
| Met | Ala | Glu | Leu | Arg | Ile | Tyr | Gln | Asn | Ala | Asn | Glu | Gly | Lys | Trp | Leu | 195 | 200 | 205 |     |
| Thr | Ala | Asn | Arg | Glu | Phe | Thr | Ile | Thr | Val | Tyr | Ala | Ile | Gly | Thr | Gly | 210 | 215 | 220 |     |
| Thr | Leu | Gly | Gln | His | Thr | Met | Glu | Pro | Leu | Ser | Ser | Val | Asn | Thr | Thr | 225 | 230 | 235 | 240 |
| Gly | Asp | Tyr | Val | Gly | Trp | Leu | Glu | Leu | Asn | Val | Thr | Glu | Gly | Leu | His | 245 | 250 | 255 |     |
| Glu | Trp | Leu | Val | Lys | Ser | Lys | Asp | Asn | His | Gly | Ile | Tyr | Ile | Gly | Ala | 260 | 265 | 270 |     |

His Ala Val Asn Arg Pro Asp Arg Glu Val Lys Leu Asp Asp Ile Gly  
275 280 285

Leu Ile His Arg Lys Val Asp Asp Glu Phe Gln Pro Phe Met Ile Gly  
290 295 300

Phe Phe Arg Gly Pro Glu Leu Ile Lys Ala Thr Ala His Ser Ser His  
305 310 315 320

His Arg Ser Lys Arg Ser Ala Ser His Pro Arg Lys Arg Lys Lys Ser  
325 330 335

Val Ser Pro Asn Asn Val Pro Leu Leu Glu Pro Met Glu Ser Thr Arg  
340 345 350

Ser Cys Gln Met Gln Thr Leu Tyr Ile Asp Phe Lys Asp Leu Gly Trp  
355 360 365

His Asp Trp Ile Ile Ala Pro Glu Gly Tyr Gly Ala Phe Tyr Cys Ser  
370 375 380

Gly Glu Cys Asn Phe Pro Leu Asn Ala His Met Asn Ala Thr Asn His  
385 390 395 400

Ala Ile Val Gln Thr Leu Val His Leu Leu Glu Pro Lys Lys Val Pro  
405 410 415

Lys Pro Cys Cys Ala Pro Thr Arg Leu Gly Ala Leu Pro Val Leu Tyr  
420 425 430

His Leu Asn Asp Glu Asn Val Asn Leu Lys Lys Tyr Arg Asn Met Ile  
435 440 445

Val Lys Ser Cys Gly Cys His  
450 455

(2) INFORMATION FOR SEQ ID NO:26:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: amino acids
  - (B) TYPE: amino acid
  - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: protein
- (iii) ORIGINAL SOURCE:
  - (A) ORGANISM: Homo Sapiens
- (ix) FEATURE:
  - (A) NAME/KEY: Protein
  - (B) LOCATION: 1..102
  - (D) OTHER INFORMATION: /note="BMP3"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:26:

(i)SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 104 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii)MOLECULE TYPE: protein

(ix)FEATURE:

- (A) NAME/KEY: Protein
- (B) LOCATION: 1..104
- (D) OTHER INFORMATION: /note="BMP3"

(xi)SEQUENCE DESCRIPTION: SEQ ID NO:26:

```

Cys Ala Arg Arg Tyr Leu Lys Val Asp Phe Ala Asp Ile Gly Trp Ser
1 5 10 15
Glu Trp Ile Ile Ser Pro Lys Ser Phe Asp Ala Tyr Try Cys Ser Gly
 20 25 30
Ala Cys Gln Phe Pro Met Pro Lys Ser Leu Lys Pro Ser Asn His Ala
 35 40 45
Thr Ile Gln Ser Ile Val Ala Arg Ala Val Gly Val Val Pro Gly Ile
 50 55 60
Pro Glu Pro Cys Cys Val Pro Glu Lys Met Ser Ser Leu Ser Ile Leu
65 70 75 80
Phe Phe Asp Glu Asn Lys Asn Val Val Leu Lys Val Tyr Pro Asn Met
 85 90 95
Thr Val Glu Ser Cys Ala Cys Arg
 100

```

(2) INFORMATION FOR SEQ ID NO:27:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 102 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(vi) ORIGINAL SOURCE:

- (A) ORGANISM: HOMO SAPIENS

(ix) FEATURE:

- (A) NAME/KEY: Protein

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(B) LOCATION: 1..102  
(D) OTHER INFORMATION: /note= "BMP5"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:27:

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Cys | Lys | Lys | His | Glu | Leu | Tyr | Val | Ser | Phe | Arg | Asp | Leu | Gly | Trp | Gln |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |
| Asp | Trp | Ile | Ile | Ala | Pro | Glu | Gly | Tyr | Ala | Ala | Phe | Tyr | Cys | Asp | Gly |
|     |     | 20  |     |     |     |     |     | 25  |     |     |     |     | 30  |     |     |
| Glu | Cys | Ser | Phe | Pro | Leu | Asn | Ala | His | Met | Asn | Ala | Thr | Asn | His | Ala |
|     |     | 35  |     |     |     |     | 40  |     |     |     |     | 45  |     |     |     |
| Ile | Val | Gln | Thr | Leu | Val | His | Leu | Met | Phe | Pro | Asp | His | Val | Pro | Lys |
|     | 50  |     |     |     |     | 55  |     |     |     |     | 60  |     |     |     |     |
| Pro | Cys | Cys | Ala | Pro | Thr | Lys | Leu | Asn | Ala | Ile | Ser | Val | Leu | Tyr | Phe |
| 65  |     |     |     |     | 70  |     |     |     |     | 75  |     |     |     |     | 80  |
| Asp | Asp | Ser | Ser | Asn | Val | Ile | Leu | Lys | Lys | Tyr | Arg | Asn | Met | Val | Val |
|     |     |     |     | 85  |     |     |     |     | 90  |     |     |     |     | 95  |     |
| Arg | Ser | Cys | Gly | Cys | His |     |     |     |     |     |     |     |     |     |     |
|     |     |     | 100 |     |     |     |     |     |     |     |     |     |     |     |     |

(2) INFORMATION FOR SEQ ID NO:28:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 102 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: protein
- (vi) ORIGINAL SOURCE:
  - (A) ORGANISM: HOMO SAPIENS
- (ix) FEATURE:
  - (A) NAME/KEY: Protein
  - (B) LOCATION: 1..102
  - (D) OTHER INFORMATION: /note= "BMP6"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:28:

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Cys | Arg | Lys | His | Glu | Leu | Tyr | Val | Ser | Phe | Gln | Asp | Leu | Gly | Trp | Gln |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |
| Asp | Trp | Ile | Ile | Ala | Pro | Lys | Gly | Tyr | Ala | Ala | Asn | Tyr | Cys | Asp | Gly |
|     |     | 20  |     |     |     |     |     | 25  |     |     |     |     | 30  |     |     |
| Glu | Cys | Ser | Phe | Pro | Leu | Asn | Ala | His | Met | Asn | Ala | Thr | Asn | His | Ala |

(2) INFORMATION FOR SEQ ID NO:29:

(A) LENGTH: 102 amino acids  
(B) TYPE: amino acid  
(D) TOPOLOGY: linear

(ix) FEATURE:

(A) NAME/KEY: Protein  
(B) LOCATION: 1..102  
(D) OTHER INFORMATION: /label= OPX  
/note= "WHEREIN XAA AT EACH POS'N IS INDEPENDENTLY  
SELECTED FROM THE RESIDUES OCCURRING AT THE  
CORRESPONDING POS'N IN THE C-TERMINAL SEQUENCE OF MOUSE  
OR HUMAN OP1 OR OP2 (SEE SEQ. ID NOS. 5,6,7 and 8 or  
16,18,20 and 22.)"

Cys Xaa Xaa His Glu Leu Tyr Val Xaa Phe Xaa Asp Leu Gly Trp Xaa  
1 5 10 15

Asp Trp Xaa Ile Ala Pro Xaa Gly Tyr Xaa Ala Tyr Tyr Cys Glu Gly  
20 25 30

Glu Cys Xaa Phe Pro Leu Xaa Ser Xaa Met Asn Ala Thr Asn His Ala  
35 40 45

Ile Xaa Gln Xaa Leu Val His Xaa Xaa Xaa Pro Xaa Xaa Val Pro Lys  
50 55 60

Xaa Cys Cys Ala Pro Thr Xaa Leu Xaa Ala Xaa Ser Val Leu Tyr Xaa  
65 70 75 80

Asp Xaa Ser Xaa Asn Val Xaa Leu Xaa Lys Xaa Arg Asn Met Val Val  
85 90 95

Xaa Ala Cys Gly Cys His  
100

(2) INFORMATION FOR SEQ ID NO:30:

(i)SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 97 amino acids
- (B) TYPE: amino acids
- (C) TOPOLOGY: linear

(ii)MOLECULE TYPE: protein

(ix)FEATURE:

- (A) NAME: Generic Sequence 5
- (D) OTHER INFORMATION: wherein each Xaa is independently selected from a group of one or more specified amino acids as defined in the specification.

(xi)SEQUENCE DESCRIPTION: SEQ ID NO:30:

Leu Xaa Xaa Xaa Phe  
1 5  
Xaa Xaa Xaa Gly Trp Xaa Xaa Trp Xaa  
10  
Xaa Xaa Pro Xaa Xaa Xaa Xaa Ala  
15 20  
Xaa Tyr Cys Xaa Gly Xaa Cys Xaa  
25 30  
Xaa Pro Xaa Xaa Xaa Xaa Xaa  
35  
Xaa Xaa Xaa Asn His Ala Xaa Xaa  
40 45  
Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa  
50  
Xaa Xaa Xaa Xaa Xaa Xaa Xaa Cys  
55 60  
Cys Xaa Pro Xaa Xaa Xaa Xaa Xaa  
65  
Xaa Xaa Xaa Leu Xaa Xaa Xaa  
70 75  
Xaa Xaa Xaa Xaa Val Xaa Leu Xaa  
80  
Xaa Xaa Xaa Xaa Met Xaa Val Xaa  
85 90  
Xaa Cys Xaa Cys Xaa  
95

(2) INFORMATION FOR SEQ ID NO:31:

(i)SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 102 amino acids
- (B) TYPE: amino acids
- (C) TOPOLOGY: linear

(ii)MOLECULE TYPE: protein

(ix)FEATURE:

- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:31:

(2) INFORMATION FOR SEQ ID NO:32:

- ```
/note= "GDF-1 CDNA"
```


- (x) PUBLICATION INFORMATION:
 (A) AUTHORS: Lee, Se-Jin
 (B) TITTLE: Expression of Growth/Differentiation Factor 1
 (C) JOURNAL: Proc. Nat'l Acad. Sci.
 (D) VOLUME: 88
 (E) RELEVANT RESIDUES: 1-1238
 (F) PAGES: 4250-4254
 (G) DATE: May-1991
 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:32:

GGGGACACCG	GGCCCGCCCT	CAGCCCACTG	GTCCCGGGCC	GCCGCGGACC	CTGCGCACTC	60
TCTGGTCATC	GCCTGGGAGG	AAG ATG CCA CCG CCG CAG CAA GGT CCC TGC GGC	113			
		Met Pro Pro Pro Gln Gln Gly Pro Cys Gly				
		1 5 10				
CAC CAC CTC CTC CTC CTC CTG GCC CTG CTG CTG CCC TCG CTG CCC	158					
His His Leu Leu Leu Leu Leu Ala Leu Leu Leu Pro Ser Leu Pro						
	15 20 25					
CTG ACC CGC GCC CCC GTG CCC CCA GGC CCA GCC GCC GCC CTG CTC	203					
Leu Thr Arg Ala Pro Val Pro Pro Gly Pro Ala Ala Ala Leu Leu						
	30 35 40					
CAG GCT CTA GGA CTG CGC GAT GAG CCC CAG GGT GCC CCC AGG CTC	248					
Gln Ala Leu Gly Leu Arg Asp Glu Pro Gln Gly Ala Pro Arg Leu						
	45 50 55					
CGG CCG GTT CCC CCG GTC ATG TGG CGC CTG TTT CGA CGC CGG GAC	293					
Arg Pro Val Pro Pro Val Met Trp Arg Leu Phe Arg Arg Arg Asp						
	60 65 70					
CCC CAG GAG ACC AGG TCT GGC TCG CGG CGG ACG TCC CCA GGG GTC	338					
Pro Gln Glu Thr Arg Ser Gly Ser Arg Arg Thr Ser Pro Gly Val						
	75 80 85					
ACC CTG CAA CCG TGC CAC GTG GAG GAG CTG GGG GTC GCC GGA AAC	383					
Thr Leu Gln Pro Cys His Val Glu Glu Leu Gly Val Ala Gly Asn						
	90 95 100					
ATC GTG CGC CAC ATC CCG GAC CGC GGT GCG CCC ACC CGG GCC TCG	428					
Ile Val Arg His Ile Pro Asp Arg Gly Ala Pro Thr Arg Ala Ser						
	105 110 115					
GAG CCT GTC TCG GCC GCG GGG CAT TGC CCT GAG TGG ACA GTC GTC	473					
Glu Pro Val Ser Ala Ala Gly His Cys Pro Glu Trp Thr Val Val						
	120 125 130					
TTC GAC CTG TCG GCT GTG GAA CCC GCT GAG CGC CCG AGC CGG GCC	518					
Phe Asp Leu Ser Ala Val Glu Pro Ala Glu Arg Pro Ser Arg Ala						
	135 140 145					

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CGC	CTG	GAG	CTG	CCT	TTC	GCG	GCG	GCG	GCG	GCA	GCC	CCG	GAG		563
Arg	Leu	Glu	Leu	Arg	Phe	Ala	Ala	Ala	Ala	Ala	Ala	Pro	Glu		
				150						155			160		
GGC	GGC	TGG	GAG	CTG	AGC	GTG	GCG	CAA	GCG	GGC	CAG	GGC	GCG	GGC	608
Gly	Gly	Trp	Glu	Leu	Ser	Val	Ala	Gln	Ala	Gly	Gln	Gly	Ala	Gly	
				165					170					175	
GCG	GAC	CCC	GGG	CCG	GTG	CTG	CTC	CGC	CAG	TTG	GTG	CCC	GCC	CTG	653
Ala	Asp	Pro	Gly	Pro	Val	Leu	Leu	Arg	Gln	Leu	Val	Pro	Ala	Leu	
				180					185					190	
GGG	CCG	CCA	GTG	CGC	GCG	GAG	CTG	CTG	GGC	GCC	GCT	TGG	GCT	CGC	698
Gly	Pro	Pro	Val	Arg	Ala	Glu	Leu	Leu	Gly	Ala	Ala	Trp	Ala	Arg	
				195					200					205	
AAC	GCC	TCA	TGG	CCG	CGC	AGC	CTC	CGC	CTG	GCG	CTG	GCG	CTA	CGC	743
Asn	Ala	Ser	Trp	Pro	Arg	Ser	Leu	Arg	Leu	Ala	Leu	Ala	Leu	Arg	
				210					215					220	
CCC	CGG	GCC	CCT	GCC	GCC	TGC	GCG	CGC	CTG	GCC	GAG	GCC	TCG	CTG	788
Pro	Arg	Ala	Pro	Ala	Ala	Cys	Ala	Arg	Leu	Ala	Glu	Ala	Ser	Leu	
				225					230					235	
CTG	CTG	GTG	ACC	CTC	GAC	CCG	CGC	CTG	TGC	CAC	CCC	CTG	GCC	CGG	833
Leu	Leu	Val	Thr	Leu	Asp	Pro	Arg	Leu	Cys	His	Pro	Leu	Ala	Arg	
				240					245					250	
CCG	CGG	CGC	GAC	GCC	GAA	CCC	GTG	TTG	GGC	GGC	GGC	CCC	GGG	GGC	878
Pro	Arg	Arg	Asp	Ala	Glu	Pro	Val	Leu	Gly	Gly	Gly	Pro	Gly	Gly	
				255					260					265	
GCT	TGT	CGC	GCG	CGG	CGG	CTG	TAC	GTG	AGC	TTC	CGC	CAG	GTG	GGC	923
Ala	Cys	Arg	Ala	Arg	Arg	Leu	Tyr	Val	Ser	Phe	Arg	Glu	Val	Gly	
				270					275					280	
TGG	CAC	CGC	TGG	GTC	ATC	GCG	CCG	CGC	CCC	TTC	CTG	GCC	AAC	TAC	968
Trp	His	Arg	Trp	Val	Ile	Arg	Pro	Arg	Gly	Phe	Leu	Ala	Asn	Tyr	
				285					290					295	
TGC	CAG	GGT	CAG	TGC	GCG	CTG	CCC	GTC	GCG	CTG	TCG	GGG	TCC	GGG	1013
Cys	Gln	Gly	Gln	Cys	Ala	Leu	Pro	Val	Ala	Leu	Ser	Gly	Ser	Gly	
				300					305					310	
GGG	CCG	CCG	GCG	CTC	AAC	CAC	GCT	GTG	CTG	CGC	GCG	CTC	ATG	CAC	1058
Gly	Pro	Pro	Ala	Leu	Asn	His	Ala	Val	Leu	Arg	Ala	Leu	Met	His	
				315					320					325	
GCG	GCC	GCC	CCG	GGA	GCC	GCC	GAC	CTG	CCC	TGC	TGC	GTG	CCC	GCG	1103
Ala	Ala	Ala	Pro	Gly	Ala	Ala	Asp	Leu	Pro	Cys	Cys	Val	Pro	Ala	
				330					335					340	
CGC	CTG	TCG	CCC	ATC	TCC	GTG	CTC	TTC	TTT	GAC	AAC	AGC	GAC	AAC	1148

[illegible]

(2) INFORMATION FOR SEQ ID NO:33:

- ```
(i) SEQUENCE CHARACTERISTICS:
 (A) LENGTH: 372 amino acids
 (B) TYPE: amino acid
 (C) STRANDEDNESS: single
 (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(vi) ORIGINAL SOURCE:
 (A) ORGANISM: human
 (F) TISSUE TYPE: BRAIN

(ix) FEATURE:
 (A) NAME/KEY: CDS
 (B) LOCATION:
 (D) OTHER INFORMATION: /function=
 /product= "GDF-1"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:33:
```

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
|     |     |     |     |     |     | Met | Pro | Pro | Pro | Gln | Gln | Gly | Pro | Cys | Gly |
|     |     |     |     |     |     | 1   |     |     |     | 5   |     |     |     |     | 10  |
| His | His | Leu | Leu | Leu | Leu | Leu | Ala | Leu | Leu | Leu | Pro | Ser | Leu | Pro |     |
|     |     |     |     | 15  |     |     |     |     | 20  |     |     |     |     | 25  |     |
| Leu | Thr | Arg | Ala | Pro | Val | Pro | Pro | Gly | Pro | Ala | Ala | Ala | Leu | Leu |     |
|     |     |     |     | 30  |     |     |     |     | 35  |     |     |     |     | 40  |     |
| Gln | Ala | Leu | Gly | Leu | Arg | Asp | Glu | Pro | Gln | Gly | Ala | Pro | Arg | Leu |     |
|     |     |     |     | 45  |     |     |     |     | 50  |     |     |     |     | 55  |     |
| Arg | Pro | Val | Pro | Pro | Val | Met | Trp | Arg | Leu | Phe | Arg | Arg | Arg | Asp |     |
|     |     |     |     | 60  |     |     |     |     | 65  |     |     |     |     | 70  |     |





What is claimed is:

1. A method for alleviating the tissue destructive effects associated with the inflammatory response to tissue injury in a mammal, the method comprising the step of:

providing to the injured tissue a therapeutically effective concentration of a morphogen sufficient to substantially inhibit or reduce the tissue damage resulting from said inflammatory response.

2. The method of claim 1 where said step of providing a therapeutically effective morphogen concentration to said injured tissue comprises the step of administering a therapeutically effective concentration of a morphogen to said mammal.
3. The method of claim 1 where said step of providing a therapeutically effective morphogen concentration to said injured tissue comprises the step of administering to said mammal an agent that stimulates in vivo a therapeutically effective concentration of an endogenous morphogen.
4. The method of claim 1 wherein said step of providing a therapeutically effective concentration of a morphogen is conducted prior to reduction or interruption of blood flow to the tissue.
5. The method of claim 1 wherein said step of providing a therapeutically effective concentration of a morphogen is conducted after

reduction or interruption of blood flow to the tissue and before reperfusion.

6. The method of claim 1 wherein said step of providing a therapeutically effective concentration of a morphogen is conducted following ischemia-reperfusion injury.
7. The method of claim 1 wherein said said step of providing a therapeutically effective concentration of a morphogen is conducted following hyperoxia injury.
8. The method of claim 1 wherein said morphogen is provided to said tissue prior to said tissue injury.
9. The method of claim 1 wherein said step of providing a therapeutically effective concentration of a morphogen is conducted prior to ischemia-reperfusion injury.
10. The method of claim 1 wherein said tissue damage results from an abnormal immune response in said mammal.
11. The method of claim 1 wherein said tissue damage is associated with an inflammatory disease.
12. The method of claim 11 wherein said inflammatory disease is an autoimmune disease.
13. The method of claim 11 wherein said inflammatory disease comprises arthritis, psoriasis, dermatitis or diabetes.

14. The method of claim 13 wherein said arthritis is rheumatoid, degenerative or psoriatic arthritis.
15. The method of claim 12 wherein said inflammatory disease comprises an airway inflammation in a mammal.
16. The method of claim 15 wherein said airway inflammation comprises chronic bronchitis, emphysema, idiopathic pulmonary fibrosis or asthma.
17. The method of claim 12 wherein inflammatory disease comprises a generalized acute inflammatory response.
18. The method of claim 17 herein said inflammatory disease comprises adult respiratory distress syndrome.
19. The method of claim 1 wherein said tissue damage is to a transplanted organ or tissue.
20. A method for reducing tissue damage associated with ischemia-reperfusion injury in a human, the method comprising the step of:  
  
providing to the injured tissue a therapeutic concentration of a morphogen sufficient to alleviate the damage associated with said injury.
21. A method for reducing the tissue damage associated with hyperoxia injury in a human, the method comprising the step of:

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providing to the injured tissue a therapeutic concentration of a morphogen sufficient to alleviate the damage associated with said injury.

22. The method of claim 20 or 21 wherein said step of providing a therapeutically effective morphogen concentration to said injured tissue comprises the step of administering a therapeutically effective concentration of a morphogen to said mammal.
23. The method of claim 20 or 21 wherein said step of providing a therapeutically effective morphogen concentration to said injured tissue comprises the step of administering to said mammal an agent that stimulates in vivo a therapeutically effective concentration of an endogenous morphogen.
24. The method of claim 1, 20 or 21 wherein said tissue is lung tissue, cardiac tissue, hepatic tissue or renal tissue.
25. The method of claim 6, 9, or 20 wherein said ischemic-reperfusion injury results from cardiac arrest, preliminary occlusion, arterial occlusion, coronary occlusion or occlusive stroke.
26. The method of claim 1, 20 or 21 wherein said morphogen comprises an amino acid sequence sharing at least 70% homology with one of the sequences selected from the group consisting of: OP-1, OP-2, CBMP2, Vg1(fx), Vgr(fx), DPP(fx), GDF-1(fx) and 60A(fx).
27. The method of claim 26 wherein said morphogen comprises an amino acid sequence sharing a last

80% homology with one of the sequences selected from the group consisting of: OP-1, OP-2, CBMP2, BMP3(fx), BMP5(fx), BMP6(fx), Vg1(fx), Vgr(fx), DPP(fx), GDF-1(fx) and 60A(fx).

28. The method of claim 1, 20 or 21 wherein said morphogen comprises an amino acid sequence having greater than 60% amino acid identity with the sequence defined by residues 43-139 of Seq. ID No. 5 (hOP1).
29. The method of claim 28 wherein said morphogen comprises an amino acid sequence having greater than 65% amino acid identity with the sequence defined by residues 43-139 of Seq. ID No. 5 (hOP1).
30. The method of claim 29 wherein said morphogen comprises an amino acid sequence defined by residues 43-139 of Seq. ID No. 5 (hOP1), including allelic and species variants thereof.
31. The method of claim 1, 20 or 21 wherein said morphogen comprises an amino acid sequence defined by Generic Sequences 1, 2, 3, 4, 5 or 6 (Seq. ID Nos. 1, 2, 3, 4, 30 or 31).
32. The method of claim 1, 20 or 21 wherein said morphogen comprises an amino acid sequence defined by OPX (Seq. ID No. 29).
33. A method for reducing the tissue injury associated with the reduction or interruption of blood flow to an organ or tissue in a clinical procedure, the method comprising the step of providing a therapeutic concentration of a morphogen to said

organ or tissue prior to the interruption of blood flow.

34. A method for reducing the tissue injury associated with the reduction or interruption of blood flow to an organ or tissue in a clinical procedure, the method comprising the step of providing a therapeutic concentration of a morphogen to said organ or tissue after the reduction or interruption of blood flow to said organ or tissue.
35. The method of claim 33 or 34 wherein said clinical procedure is a carotid enterectomy, a coronary artery bypass, a tissue grafting procedure, an organ transplant, or a fibrinolytic therapy.
36. The method of claim 33 or 34 wherein said morphogen is administered parenterally.
37. The method of claim 33 or 34 wherein said morphogen is administered prophylactically.
38. A pharmaceutical composition for use in alleviating the injury associated with tissue exposure to toxic oxygen concentrations comprising a therapeutically effective amount of a morphogen in admixture with a free oxygen radical inhibiting agent or an anticoagulant.
39. A pharmaceutical composition for topical administration comprising a therapeutically effective concentration of a morphogen in admixture with a dermatologically acceptable carrier.

40. A pharmaceutical composition for topical administration to a tissue comprising a therapeutically effective concentration of a morphogen dispersed in a biocompatible, non-irritating tissue surface adhesive.
41. The composition of claim 40 wherein said adhesive comprises hydroxypropylcellulose.
42. The composition of claim 38, 39 or 40 wherein said morphogen comprises an amino acid sequence sharing at least 70% homology with one of the sequences selected from the group consisting of: OP-1, OP-2, CBMP2, Vgl(fx), Vgr(fx), DPP(fx), GDF-1(fx) and 60A(fx).
43. The composition of claim 42 wherein said morphogen comprises an amino acid sequence sharing a last 80% homology with one of the sequences selected from the group consisting of: OP-1, OP-2, CBMP2, BMP3(fx), BMP5(fx), BMP6(fx), Vgl(fx), Vgr(fx), DPP(fx), GDF-1(fx) and 60A(fx).
44. The composition of claim 38, 39 or 40 wherein said morphogen comprises an amino acid sequence having greater than 60% amino acid identity with the sequence defined by residues 43-139 of Seq. ID No. 5 (hOP1).
45. The composition of claim 44 wherein said morphogen comprises an amino acid sequence having greater than 65% amino acid identity with the sequence defined by residues 43-139 of Seq. ID No. 5 (hOP1).

46. The composition of claim 45 wherein said morphogen comprises an amino acid sequence defined by residues 43-139 of Seq. ID No. 5 (hOP1), including allelic and species variants thereof.
47. The composition of claim 38, 39 or 40 wherein said morphogen comprises an amino acid sequence defined by Generic Sequences 1, 2, 3, 4, 5 or 6 (Seq. ID Nos. 1, 2, 3, 4, 30 or 31).
48. The composition of claim 38, 39 or 40 wherein said morphogen comprises an amino acid sequence defined by OPX (Seq. ID No. 29).

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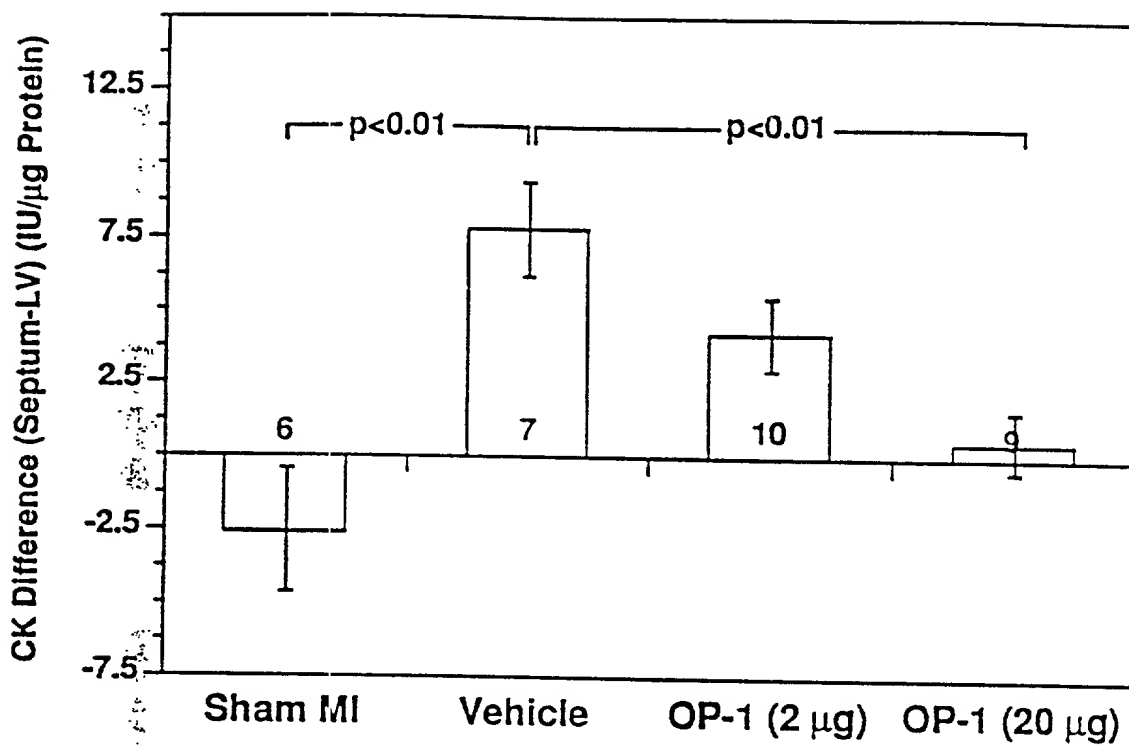


FIG. 1

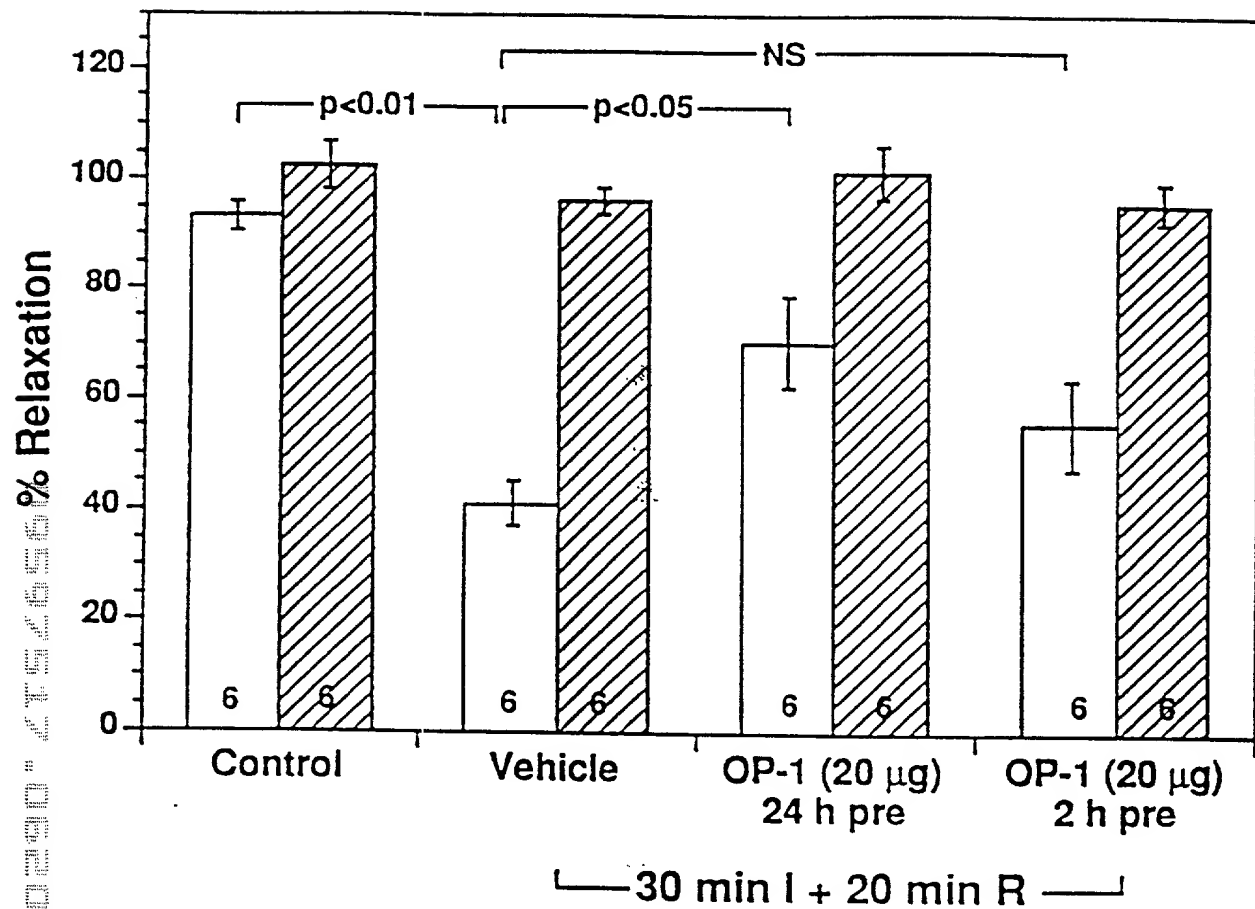


FIG. 2



PMNs per Field

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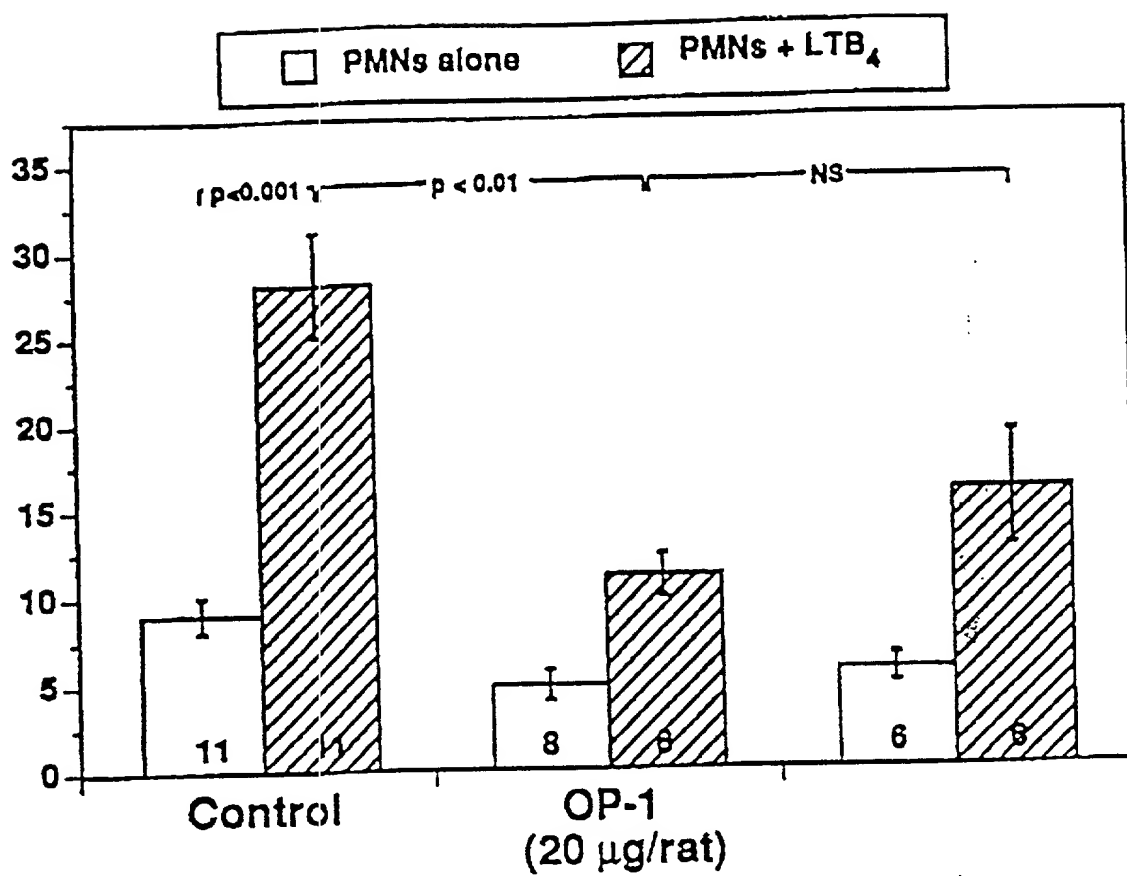
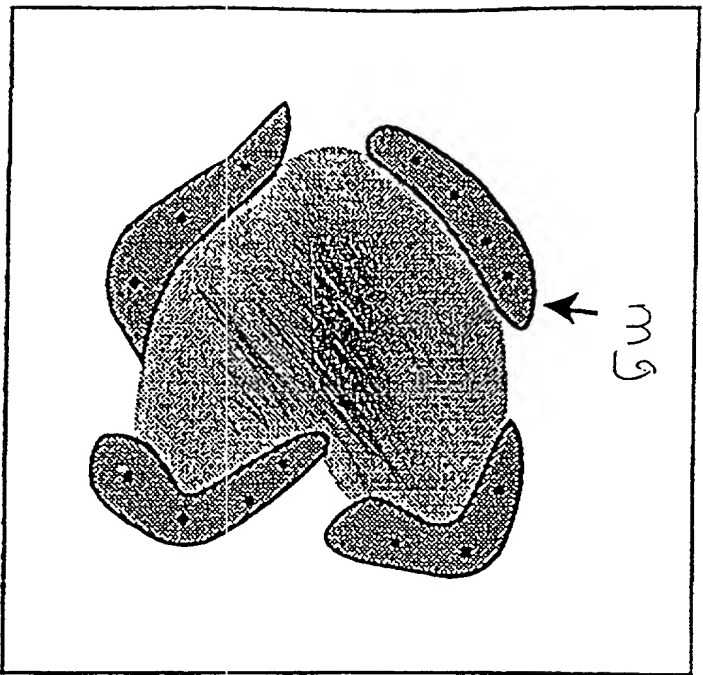
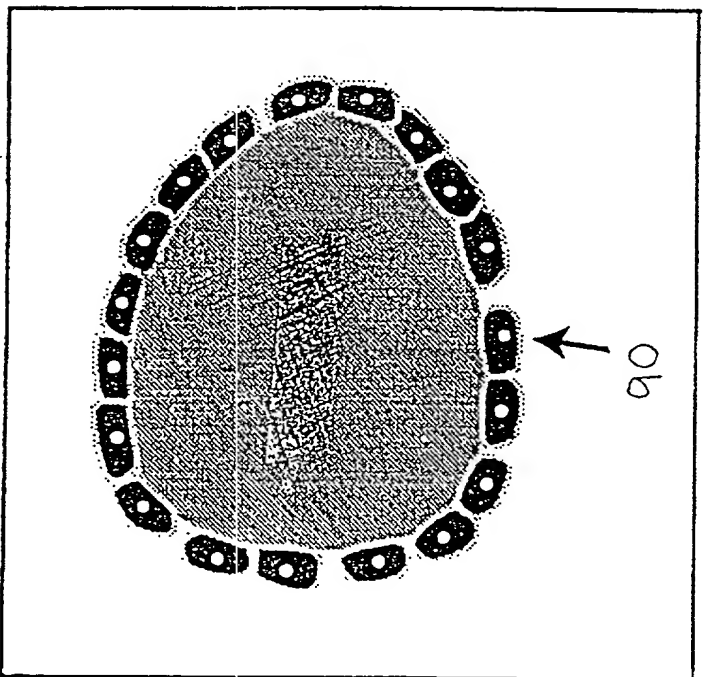


FIG. 3

Fig. 4



A



B

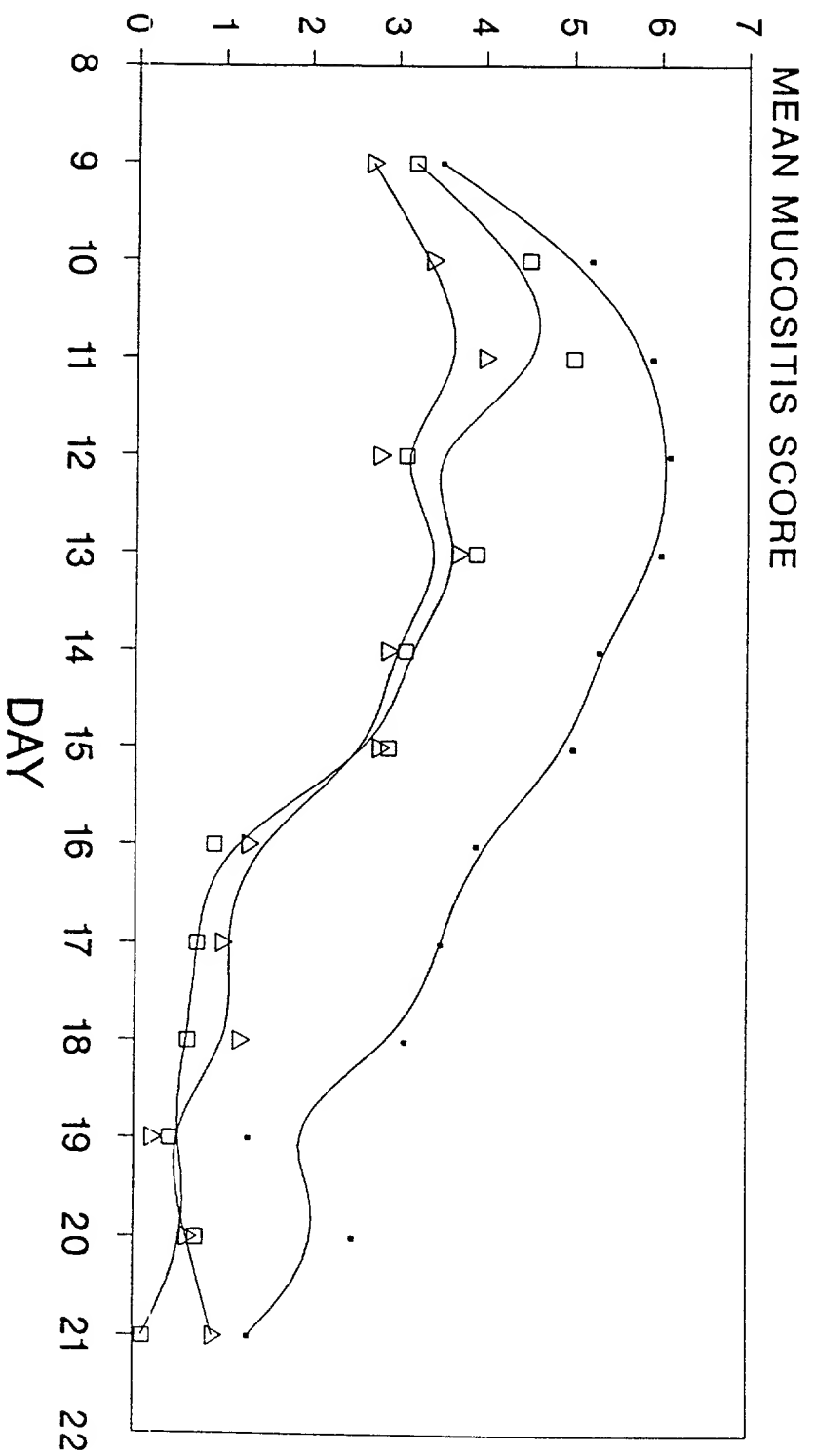


Fig. 5

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FIG 6A

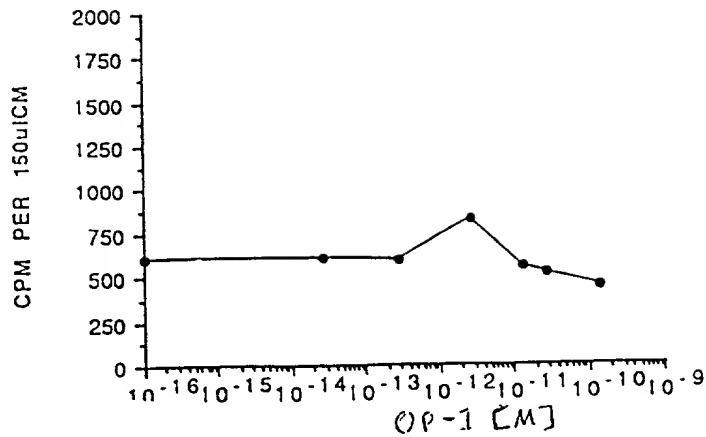


FIG. 6B

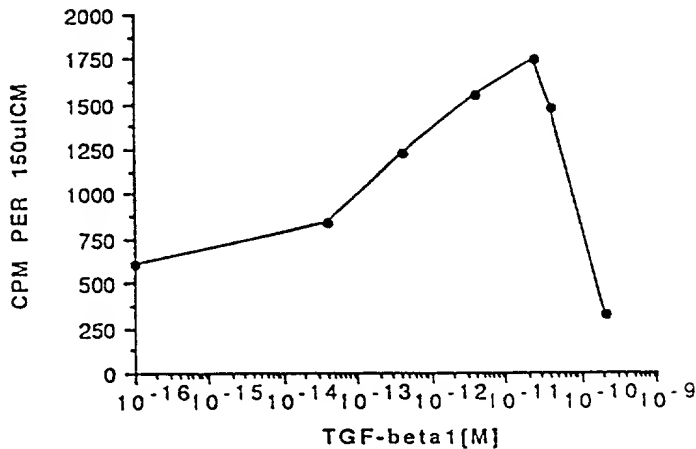


FIG 6C

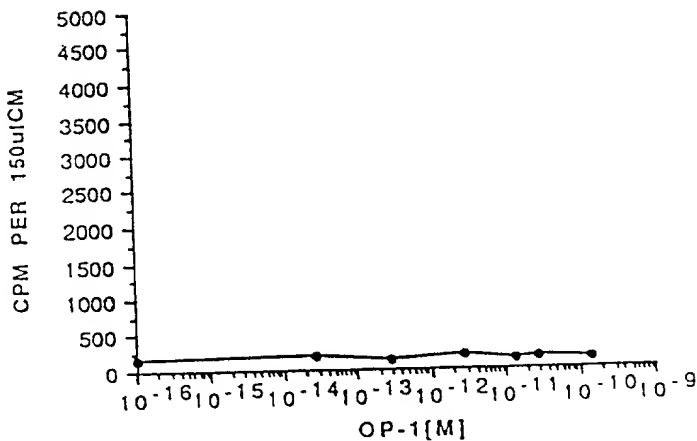
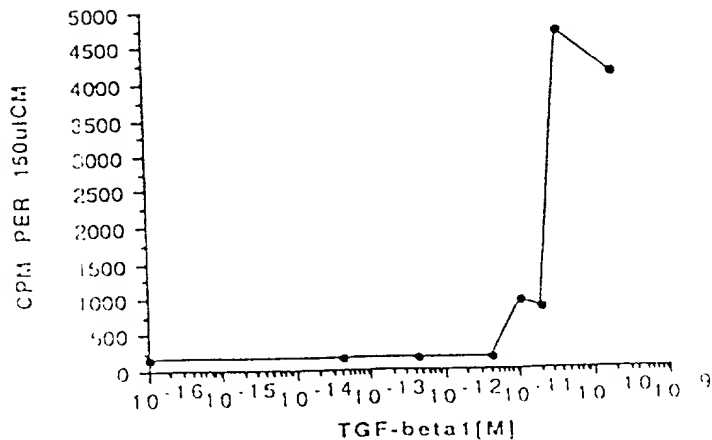


FIG. 6D



---

COMBINED DECLARATION AND POWER OF ATTORNEY  
FOR PATENT APPLICATION

(Original, Design, National Stage of PCT, Supplemental,  
Divisional, Continuation or CIP)

---

As a below named inventor, I hereby declare that:

TYPE OF DECLARATION

This declaration is of the following type: (check one  
applicable item below)

- ☒ original  
☐ design  
☐ supplemental  
☐ national stage of PCT  
☐ divisional  
☐ continuation  
☐ continuation-in-part (CIP)

INVENTORSHIP IDENTIFICATION

My residence, post office address and citizenship are as  
stated below next to my name, I believe I am the original, first  
and sole inventor (if only one name is listed below) or an  
original, first and joint inventor (if plural names are listed  
below) of the subject matter which is claimed and for which a  
patent is sought on the invention entitled:

TITLE OF INVENTION

MORPHOGEN-INDUCED MODULATION OF INFLAMMATORY RESPONSE

---



EARLIEST FOREIGN APPLICATION(S), IF ANY FILED WITHIN  
12 MONTHS (6 MONTHS FOR DESIGN) PRIOR TO  
THIS U.S. APPLICATION

| Country | Application<br>Number | Date of Filing<br>(mo., day, year) | Priority Claimed<br>Under 37 USC 119                                                           |
|---------|-----------------------|------------------------------------|------------------------------------------------------------------------------------------------|
| U.S.    | 92/01968              | 3/11/92                            | <input type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> X |
|         |                       |                                    | <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/>              |
|         |                       |                                    | <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/>              |

ALL FOREIGN APPLICATION(S), IF ANY FILED MORE THAN  
12 MONTHS (6 MONTHS FOR DESIGN) PRIOR TO  
THIS U.S. APPLICATION

CLAIM FOR BENEFIT OF EARLIER U.S./PCT APPLICATION(S)

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) or PCT international application(s) designating the United States of America that is/are listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, §1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application. As to subject matter of this application which is common to my earlier United States application, if any, described below, I do not believe that the same was ever known or used in the United States before my invention thereof or patented or described in any printed publication in any country before my invention thereof or more than one year prior to said earlier application, or in public use or on sale in the United States more than one year prior to said earlier application, that the said common subject

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[illegible]

|                          |               |                                                  |
|--------------------------|---------------|--------------------------------------------------|
| 753,059                  | 8/30/91       | PENDING                                          |
| (Application Serial No.) | (Filing Date) | (Status)                                         |
| 752,764                  | 8/30/91       | (patented, pending, aband.)<br>PENDING           |
| (Application Serial No.) | (Filing Date) | (Status)                                         |
| 667,274                  | 3/11/91       | (patented, pending, aband.)<br>PENDING           |
| (Application Serial No.) | (Filing Date) | (Status)                                         |
|                          | 8/28/92       | (patented, pending, aband.)<br>PENDING (CRP-068) |
| (Application Serial No.) | (Filing Date) | (Status)                                         |
|                          |               | (patented, pending, aband.)                      |

[illegible]

As a named inventor, I hereby appoint the following attorneys and/or agents to prosecute this application and transact all business in the United States Patent and Trademark Office connected therewith:

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|-----------------------|-------------------|
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| Kathleen A. Williams, | Reg. No. 34,380   |
| Robin D. Kelley,      | Reg. No. 34,637   |
| Kristofer E. Elbing,  | Reg. No. 34,590   |
| Robert J. Tosti,      | Reg. No. 35,393   |
| Madeline I. Johnston, | Reg. No. P-36,174 |
| Douglas J. Kline,     | Reg. No. 35,574   |

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Creative BioMolecules, Inc  
35 South Street  
Hopkinton, MA 01748



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Robin D. Kelley (617) 248-74777

(name and telephone number)

Wherefore I petition that letters patent be granted to me for the invention or discovery described and claimed in the attached specification and claims, and hereby subscribe my name to said specification and claims and to the foregoing declaration, power of attorney, and this petition.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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WHICH FORM A PART OF THIS DECLARATION

- X   Signature for third and subsequent joint inventors.  
Number of pages added   2  .
- Signature by administrator(trix), executor(trix) or  
legal representative for deceased or incapacitated  
inventor. Number of pages added      .
- Signature for inventor who refuses to sign or cannot  
be reached by person authorized under 37 CFR 1.47.  
Number of pages added      .
- Added pages to combined declaration and power of  
attorney for divisional, continuation, or continuation  
in-part (CIP) application.       Number of pages added.
- Authorization of attorney(s) to accept and follow  
instructions from representative.

If no further pages form a part of this Declaration then end this Declaration with this page and check the following item.

- \_\_\_\_ This declaration ends with this page.

ADDED PAGES FOR ADDITIONAL INVENTORS

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Full name of inventor

Citizenship

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Full name of inventor

Citizenship

Inventor's signature

Date

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Residence

Same as above.

Post Office Address

299RDK2054/28.bnl

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

|                 |                                                     |           |                    |
|-----------------|-----------------------------------------------------|-----------|--------------------|
| APPLICANTS :    | Kuberasampath <i>et al.</i>                         |           |                    |
| ASSIGNEE :      | Creative BioMolecules, Inc.                         |           |                    |
| SERIAL NUMBER : | C8/445,467                                          | EXAMINER: | E. Kemmerer, Ph.D. |
| FILING DATE :   | May 22, 1995                                        | ART UNIT: | 1646               |
| FOR :           | METHOD FOR REDUCING EXTRAVASATION OF EFFECTOR CELLS |           |                    |

Assistant Commissioner for Patents  
Washington, D.C. 20231

## REVOCATION BY ASSIGNEE AND NEW POWER OF ATTORNEY

CREATIVE BIOMOLECULES, INC., a company and owner of the above-identified United States patent application 08/445,467, filed May 22, 1995, the assignment, recorded in the parent case, United States patent application 07/938,336, on October 22, 1992, at Reel 6398/Frame 0976, hereby revokes any and all former powers of attorney and appoints:

| Attorney or Agent  | Registration No. | Attorney or Agent  | Registration No.    |
|--------------------|------------------|--------------------|---------------------|
| David B. Bernstein | 32,112           | A. Jason Mirabito  | 28,161              |
| David F. Crosby    | 36,400           | Michel Morency     | Limited Recognition |
| James G. Cullem    | 43,569           | John T. Prince     | 43,091              |
| Brett N. Dorny     | 35,860           | Brian Rosenbloom   | 41,276              |
| Ivor R. Elrifi     | 39,529           | Carol H. Peters    | P-45,010            |
| John A. Harre      | 37,345           | Garfield B. Simms  | P-45,109            |
| David E. Johnson   | 41,874           | Thomas M. Sullivan | 39,392              |
| Robert Klauszinski | 42,742           | Howard Susser      | 33,556              |
| Kristin E. Konzak  | P-44,848         | Shelby J. Walker   | P-45,192            |
| William Marino     | 44,219           | Martin M. Zoltick  | 35,745              |
| Leslie Meyer-Leon  | 37,381           |                    |                     |

all of MINTZ, LEVIN, COHN, FERRIS, GLOVSKY AND POPEO PC, One Financial Center, Boston, Massachusetts 02111, as Applicants' attorneys with full power of substitution and revocation to take any and all action necessary with regard to the above-identified patent.

Applicants: Kuberasamp. et al.  
U.S.S.N. 08/445,467

## SEND CORRESPONDENCE TO:

Ivor R. Elrifi  
Mintz Levin  
One Financial Center  
Boston, MA 02111

## DIRECT TELEPHONE CALLS TO:

Ivor R. Elrifi, or  
Michel Morency  
(617) 542-6000

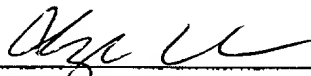
CREATIVE BIOMOLECULES, INC. certifies under 37 C.F.R. § 3.73(b) that it is the Assignee of the entire right, title and interest in the patent identified above by virtue of assignments of the patent identified above.

I, the undersigned, am empowered to act on behalf of the Assignee. Acting on behalf of the Assignee, I have reviewed all the documents in the chain of title of the patent identified above and, to the best of my knowledge and belief, title is in the Assignee identified above.

I, the undersigned, hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. § 1001 and that such willful false statements may jeopardize the validity of the patent.

Please charge any fee or any fee deficiency occasioned by this document to Deposit Account No. 50-0311, Reference No. 00960-503 CIPFWC2.

Respectfully submitted,

  
\_\_\_\_\_  
Cheryl Lawton  
Vice President, General Counsel  
CREATIVE BIOMOLECULES, INC.

Date: October 11, 1999

TRAI\OCS: 1249494.1 (qs46011.doc)

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

APPLICANTS : KUBERSAMPATH, et al.

FOR: METHOD FOR REDUCING TISSUE DAMAGE ASSOCIATED WITH  
ISCHEMIA-REPERFUSION OR HYPOXIA INJURY

Box **PATENT APPLICATION**  
Assistant Commissioner of Patents  
Washington, D.C. 20231

**STATEMENT REQUESTING USE OF PREVIOUSLY FILED SEQUENCE  
INFORMATION PURSUANT TO 37 C.F.R. 1.821(e).**

The paper copy of the Sequence Listing in the above identified patent application, filed concurrently herewith, is identical to the computer readable copy of the Sequence Listing filed in application U.S.S.N. 08/445,467 filed on May 22, 1995 entitled METHOD FOR REDUCING TISSUE DAMAGE ASSOCIATED WITH ISCHEMIA-REPERFUSION OR HYPOXIA INJURY. In accordance with 37 C.F.R. 1.821(e), please use the already filed computer readable form filed in that application as the computer readable form for the instant application. It is understood that the Patent and Trademark Office will make the necessary change in application number and filing date for the instant application. A paper copy of the Sequence Listing in said application U.S.S.N. 08/445,467 is included in a concurrently filed preliminary amendment for incorporation into the specification.

Respectfully submitted,



Ivor R. Elrifi, Reg. No. 39,529  
Ingrid A. Beattie, Reg. No. 42,306  
Attorneys for Applicants  
c/o MINTZ, LEVIN  
One Financial Center  
Boston, Massachusetts 02111  
Tel: (617) 542-6000  
Fax: (617) 542-2241

Dated: June 20, 2000  
TRADOCS:1342975.1(SS8V01!.DOC)

000290" 2T526560

SEQUENCE LISTING

(1) GENERAL INFORMATION:

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OPPERMANN, HERMANN  
RUEGER, DAVID C  
COHEN, CHARLES M  
OZKAYNAK, ENGIN  
SMART, JOHN E
- (ii) TITLE OF INVENTION: MORPHOGEN-INDUCED MODULATION OF  
INFLAMMATORY RESPONSE
- (iii) NUMBER OF SEQUENCES: 33
- (iv) CORRESPONDENCE ADDRESS:  
(A) ADDRESSEE: CREATIVE BIOMOLECULES, INC.  
(B) STREET: 35 SOUTH STREET  
(C) CITY: HOPKINTON  
(D) STATE: MA  
(E) COUNTRY: USA  
(F) ZIP: 01748
- (v) COMPUTER READABLE FORM:  
(A) MEDIUM TYPE: Floppy disk  
(B) COMPUTER: IBM PC compatible  
(C) OPERATING SYSTEM: PC-DOS/MS-DOS  
(D) SOFTWARE: PatentIn Release #1.0, Version #1.25
- (vi) CURRENT APPLICATION DATA:  
(A) APPLICATION NUMBER:  
(B) FILING DATE:  
(C) CLASSIFICATION:
- (vii) PRIOR APPLICATION DATA:  
(A) APPLICATION NUMBER: US 07/667,274  
(B) FILING DATE: 11-MAR-1991
- (vii) PRIOR APPLICATION DATA:  
(A) APPLICATION NUMBER: US 07/753,059  
(B) FILING DATE: 30-AUG-1991
- (vii) PRIOR APPLICATION DATA:  
(A) APPLICATION NUMBER: US 07/752,764  
(B) FILING DATE: 30-AUG-1991
- (viii) ATTORNEY/AGENT INFORMATION:  
(A) NAME: PITCHER ESQ, EDMUND R  
(B) REGISTRATION NUMBER: 27,829  
(C) REFERENCE/DOCKET NUMBER: CRP-059CP.APP



(ix) TELECOMMUNICATION INFORMATION:

(A) TELEPHONE: 617/248-7000

(B) TELEFAX: 617/248-7100

(2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 97 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(ix) FEATURE:

(A) NAME/KEY: Protein

(B) LOCATION: 1..97

(D) OTHER INFORMATION: /label= GENERIC-SEQ1

/note= "WHEREIN EACH XAA INDEPENDENTLY INDICATES  
ONE OF THE 20 NATURALLY-OCCURRING L-ISOMER, A-AMINO  
ACIDS, OR A DERIVATIVE THEREOF."

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Xaa | Xaa | Xaa | Xaa | Xaa | Xaa | Xaa | Xaa | Xaa | Xaa | Xaa | Xaa | Xaa | Xaa | Xaa | Xaa | Xaa |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     |     | 15  |     |
| Xaa | Xaa | Xaa | Xaa | Xaa | Xaa | Xaa | Xaa | Cys | Xaa | Xaa | Xaa | Cys | Xaa | Xaa | Xaa |     |
|     |     |     |     | 20  |     |     |     | 25  |     |     |     |     | 30  |     |     |     |
| Xaa | Xaa | Xaa | Xaa | Xaa | Xaa | Xaa | Xaa | Xaa | Xaa | Xaa | Xaa | Xaa | Xaa | Xaa | Xaa | Xaa |
|     |     |     |     | 35  |     |     |     | 40  |     |     |     |     | 45  |     |     |     |
| Xaa | Xaa | Xaa | Xaa | Xaa | Xaa | Xaa | Xaa | Xaa | Xaa | Xaa | Xaa | Cys | Cys | Xaa | Xaa |     |
|     |     |     |     | 50  |     |     |     | 55  |     |     |     |     | 60  |     |     |     |
| Xaa | Xaa | Xaa | Xaa | Xaa | Xaa | Xaa | Xaa | Xaa | Xaa | Xaa | Xaa | Xaa | Xaa | Xaa | Xaa | Xaa |
|     |     |     |     | 65  |     |     |     | 70  |     |     |     | 75  |     |     |     | 80  |
| Xaa | Xaa | Xaa | Xaa | Xaa | Xaa | Xaa | Xaa | Xaa | Xaa | Xaa | Xaa | Xaa | Cys | Xaa | Cys |     |
|     |     |     |     | 85  |     |     |     | 90  |     |     |     |     |     | 95  |     |     |
| Xaa |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |

(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 97 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(ix) FEATURE:

(A) NAME/KEY: Protein

(B) LOCATION: 1..97

(D) OTHER INFORMATION: /label= GENERIC-SEQ2

/note= "WHEREIN EACH XAA INDEPENDENTLY INDICATES  
ONE OF THE 20 NATURALLY OCCURRING L-ISOMER A-AMINO  
ACIDS, OR A DERIVATIVE THEREOF."

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa  
1 5 10 15  
Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Cys Xaa Xaa Xaa Cys Xaa Xaa Xaa  
20 25 30  
Xaa Xaa Xaa Cys Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa  
35 40 45  
Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Cys Cys Xaa Xaa  
50 55 60  
Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa  
65 70 75 80  
Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Cys Xaa Cys  
85 90 95  
Xaa

(2) INFORMATION FOR SEQ ID NO:3:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 97 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(ix) FEATURE:

(A) NAME/KEY: Protein

(B) LOCATION: 1..97

(D) OTHER INFORMATION: /label= GENERIC-SEQ3

/note= "WHEREIN EACH XAA IS INDEPENDENTLY SELECTED  
FROM A GROUP OF ONE OR MORE SPECIFIED AMINO ACIDS  
AS DEFINED IN THE SPECIFICATION."



[illegible]

(2) INFORMATION FOR SEQ ID NO:5:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 139 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(vi) ORIGINAL SOURCE:

- (A) ORGANISM: Homo sapiens  
(F) TISSUE TYPE: HIPPOCAMPUS

(ix) **FEATURE:**

- (A) NAME/KEY: Protein  
(B) LOCATION: 1..139  
(D) OTHER INFORMATION: /label= hOP1-MATURE

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

|           |           |           |            |          |           |           |           |            |           |           |           |           |            |           |           |
|-----------|-----------|-----------|------------|----------|-----------|-----------|-----------|------------|-----------|-----------|-----------|-----------|------------|-----------|-----------|
| Ser<br>1  | Thr       | Gly       | Ser        | Lys<br>5 | Gln       | Arg       | Ser       | Gln        | Asn<br>10 | Arg       | Ser       | Lys       | Thr        | Pro<br>15 | Lys       |
| Asn       | Gln       | Glu       | Ala<br>20  | Leu      | Arg       | Met       | Ala       | Asn<br>25  | Val       | Ala       | Glu       | Asn       | Ser<br>30  | Ser       | Ser       |
| Asp       | Gln       | Arg<br>35 | Gln        | Ala      | Cys       | Lys       | Lys<br>40 | His        | Glu       | Leu       | Tyr       | Val<br>45 | Ser        | Phe       | Arg       |
| Asp       | Leu<br>50 | Gly       | Trp        | Gln      | Asp       | Trp<br>55 | Ile       | Ile        | Ala       | Pro       | Glu<br>60 | Gly       | Tyr        | Ala       | Ala       |
| Tyr<br>65 | Tyr       | Cys       | Glu        | Gly      | Glu<br>70 | Cys       | Ala       | Phe        | Pro       | Leu<br>75 | Asn       | Ser       | Tyr        | Met       | Asn<br>80 |
| Ala       | Thr       | Asn       | His<br>85  | Ala      | Ile       | Val       | Gln       | Thr        | Leu<br>90 | Val       | His       | Phe       | Ile        | Asn<br>95 | Pro       |
| Glu       | Thr       | Val       | Pro<br>100 | Lys      | Pro       | Cys       | Cys       | Ala<br>105 | Pro       | Thr       | Gln       | Leu       | Asn<br>110 | Ala       | Ile       |

Ser Val Leu Tyr Phe Asp Asp Ser Ser Asn Val Ile Leu Lys Lys Tyr  
115 120 125

Arg Asn Met Val Val Arg Ala Cys Gly Cys His  
130 135

(2) INFORMATION FOR SEQ ID NO:6:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 139 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(vi) ORIGINAL SOURCE:

- (A) ORGANISM: MURIDAE
- (F) TISSUE TYPE: EMBRYO

(ix) FEATURE:

- (A) NAME/KEY: Protein
- (B) LOCATION: 1..139
- (D) OTHER INFORMATION: /label= MOP1-MATURE

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |    |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|----|
| Ser | Thr | Gly | Gly | Lys | Gln | Arg | Ser | Gln | Asn | Arg | Ser | Lys | Thr | Pro | Lys | 1   | 5   | 10  | 15 |
| Asn | Gln | Glu | Ala | Leu | Arg | Met | Ala | Ser | Val | Ala | Glu | Asn | Ser | Ser | Ser | 20  | 25  | 30  |    |
| Asp | Gln | Arg | Gln | Ala | Cys | Lys | Lys | His | Glu | Leu | Tyr | Val | Ser | Phe | Arg | 35  | 40  | 45  |    |
| Asp | Leu | Gly | Trp | Gln | Asp | Trp | Ile | Ile | Ala | Pro | Glu | Gly | Tyr | Ala | Ala | 50  | 55  | 60  |    |
| Tyr | Tyr | Cys | Glu | Gly | Glu | Cys | Ala | Phe | Pro | Leu | Asn | Ser | Tyr | Met | Asn | 65  | 70  | 75  | 80 |
| Ala | Thr | Asn | His | Ala | Ile | Val | Gln | Thr | Leu | Val | His | Phe | Ile | Asn | Pro | 85  | 90  | 95  |    |
| Asp | Thr | Val | Pro | Lys | Pro | Cys | Cys | Ala | Pro | Thr | Gln | Leu | Asn | Ala | Ile | 100 | 105 | 110 |    |
| Ser | Val | Leu | Tyr | Phe | Asp | Asp | Ser | Ser | Asn | Val | Ile | Leu | Lys | Lys | Tyr | 115 | 120 | 125 |    |
| Arg | Asn | Met | Val | Val | Arg | Ala | Cys | Gly | Cys | His | 130 | 135 |     |     |     |     |     |     |    |

0002290" 27526550

(2) INFORMATION FOR SEQ ID NO:7:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 139 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

## (ii) MOLECULE TYPE: protein

(vi) ORIGINAL SOURCE:

- (A) ORGANISM: HOMO SAPIENS  
(F) TISSUE TYPE: HIPPOCAMPUS

(ix) **FEATURE:**

- (A) NAME/KEY: Protein  
(B) LOCATION: 1..139  
(D) OTHER INFORMATION: /label= HOP2-MATURE

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

Ala Val Arg Pro Leu Arg Arg Arg Gln Pro Lys Lys Ser Asn Glu Leu  
1 5 10 15

Pro Gln Ala Asn Arg Leu Pro Gly Ile Phe Asp Asp Val His Gly Ser  
20 25 30

His Gly Arg Gln Val Cys Arg Arg His Glu Leu Tyr Val Ser Phe Gln  
35 40 45

Asp Leu Gly Trp Leu Asp Trp Val Ile Ala Pro Gln Gly Tyr Ser Ala  
50 55 60

Tyr Tyr Cys Glu Gly Glu Cys Ser Phe Pro Leu Asp Ser Cys Met Asn  
65 70 75 80

Ala Thr Asn His Ala Ile Leu Gln Ser Leu Val His Leu Met Lys Pro  
85 90 95

Asn Ala Val Pro Lys Ala Cys Cys Ala Pro Thr Lys Leu Ser Ala Thr  
100 105 110

Ser Val Leu Tyr Tyr Asp Ser Ser Asn Asn Val Ile Leu Arg Lys His  
115 120 125

Arg Asn Met Val Val Lys Ala Cys Gly Cys His  
130 135

(2) INFORMATION FOR SEQ ID NO:8:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 139 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

(vi) ORIGINAL SOURCE:

(F) TISSUE TYPE: EMBRYO

(A) NAME/KEY: Protein

(B) LOCATION: 1..139

(D) OTHER INFORMATION: /label= MOP2-MATURE

Ala Ala Arg Pro Leu Lys Arg Arg Gln Pro Lys Lys Thr Asn Glu Leu  
1 5 10 15

Pro His Pro Asn Lys Leu Pro Gly Ile Phe Asp Asp Gly His Gly Ser  
20 25 30

Arg Gly Arg Glu Val Cys Arg Arg His Glu Leu Tyr Val Ser Phe Arg  
35 40 45

Asp Leu Gly Trp Leu Asp Trp Val Ile Ala Pro Gln Gly Tyr Ser Ala  
50 55 60

Tyr Tyr Cys Glu Gly Glu Cys Ala Phe Pro Leu Asp Ser Cys Met Asn  
65 70 75 80

Ala Thr Asn His Ala Ile Leu Gln Ser Leu Val His Leu Met Lys Pro  
85 90 95

Asp Val Val Pro Lys Ala Cys Cys Ala Pro Thr Lys Leu Ser Ala Thr  
100 105 110

Ser Val Leu Tyr Tyr Asp Ser Ser Asn Asn Val Ile Leu Arg Lys His  
115 120 125

Arg Asn Met Val Val Lys Ala Cys Gly Cys His  
130 135

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 101 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(vi) ORIGINAL SOURCE:

(A) ORGANISM: bovinæ

```
(ix) FEATURE:
 (A) NAME/KEY: Protein
 (B) LOCATION: 1..101
 (D) OTHER INFORMATION: /label= CBMP-2A-FX
```

```
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

Cys Lys Arg His Pro Leu Tyr Val Asp Phe Ser Asp Val Gly Trp Asn
 1 5 10 15
Asp Trp Ile Val Ala Pro Pro Gly Tyr His Ala Phe Tyr Cys His Gly
 20 25 30
Glu Cys Pro Phe Pro Leu Ala Asp His Leu Asn Ser Thr Asn His Ala
 35 40 45
Ile Val Gln Thr Leu Val Asn Ser Val Asn Ser Lys Ile Pro Lys Ala
 50 55 60
Cys Cys Val Pro Thr Glu Leu Ser Ala Ile Ser Met Leu Tyr Leu Asp
 65 70 75 80
Glu Asn Glu Lys Val Val Leu Lys Asn Tyr Gln Asp Met Val Val Glu
 85 90 95
Gly Cys Gly Cys Arg
 100
```

(2) INFORMATION FOR SEQ ID NO:10:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 101 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: protein
- (vi) ORIGINAL SOURCE:
  - (A) ORGANISM: HOMO SAPIENS
  - (F) TISSUE TYPE: hippocampus
- (ix) FEATURE:
  - (A) NAME/KEY: Protein
  - (B) LOCATION: 1..101
  - (D) OTHER INFORMATION: /label=

```
(ix) FEATURE:
 (A) NAME/KEY: Protein
 (B) LOCATION: 1..101
 (D) OTHER INFORMATION: /label= CBMP-2B-FX
```

```
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

Cys Arg Arg His Ser Leu Tyr Val Asp Phe Ser Asp Val Gly Trp Asn
 1 5 10 15
Asp Trp Ile Val Ala Pro Pro Gly Tyr Gln Ala Phe Tyr Cys His Gly
 20 25 30
```





(2) INFORMATION FOR SEQ ID NO:12:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 102 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(vi) ORIGINAL SOURCE:

- (A) ORGANISM: XENOPUS

(ix) FEATURE:

- (A) NAME/KEY: Protein
- (B) LOCATION: 1..102
- (D) OTHER INFORMATION: /label= VGL-FX

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

Cys Lys Lys Arg His Leu Tyr Val Glu Phe Lys Asp Val Gly Trp Gln  
1                   5                   10                   15  
Asn Trp Val Ile Ala Pro Gln Gly Tyr Met Ala Asn Tyr Cys Tyr Gly  
                  20                   25                   30  
Glu Cys Pro Tyr Pro Leu Thr Glu Ile Leu Asn Gly Ser Asn His Ala  
                  35                   40                   45  
Ile Leu Gln Thr Leu Val His Ser Ile Glu Pro Glu Asp Ile Pro Leu  
50                   55                   60  
Pro Cys Cys Val Pro Thr Lys Met Ser Pro Ile Ser Met Leu Phe Tyr  
65                   70                   75                   80  
Asp Asn Asn Asp Asn Val Val Leu Arg His Tyr Glu Asn Met Ala Val  
                  85                   90                   95  
Asp Glu Cys Gly Cys Arg  
                  100

(2) INFORMATION FOR SEQ ID NO:13:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 102 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(vi) ORIGINAL SOURCE:

- (A) ORGANISM: MURIDAE

000290" 47576560

(ix) FEATURE:

- (A) NAME/KEY: Protein
- (B) LOCATION: 1..102
- (D) OTHER INFORMATION: /label= VGR-1-FX

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

Cys Lys Lys His Glu Leu Tyr Val Ser Phe Gln Asp Val Gly Trp Gln  
1                      5                      10                      15  
Asp Trp Ile Ile Ala Pro Lys Gly Tyr Ala Ala Asn Tyr Cys Asp Gly  
                    20                      25                      30  
Glu Cys Ser Phe Pro Leu Asn Ala His Met Asn Ala Thr Asn His Ala  
                    35                      40                      45  
Ile Val Gln Thr Leu Val His Val Met Asn Pro Glu Tyr Val Pro Lys  
                    50                      55                      60  
Pro Cys Cys Ala Pro Thr Lys Val Asn Ala Ile Ser Val Leu Tyr Phe  
65                      70                      75                      80  
Asp Asp Asn Ser Asn Val Ile Leu Lys Lys Tyr Arg Asn Met Val Val  
                    85                      90                      95  
Arg Ala Cys Gly Cys His  
                    100

(2) INFORMATION FOR SEQ ID NO:14:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 106 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(vi) ORIGINAL SOURCE:

- (A) ORGANISM: Homo sapiens
- (F) TISSUE TYPE: brain

(ix) FEATURE:

- (A) NAME/KEY: Protein
- (B) LOCATION: 1..106
- (D) OTHER INFORMATION: /note= "GDF-1 (fx)"

00597517.062000

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Cys | Arg | Ala | Arg | Arg | Leu | Tyr | Val | Ser | Phe | Arg | Glu | Val | Gly | Trp | His |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |
| Arg | Trp | Val | Ile | Ala | Pro | Arg | Gly | Phe | Leu | Ala | Asn | Tyr | Cys | Gln | Gly |
|     |     |     | 20  |     |     |     |     | 25  |     |     |     |     | 30  |     |     |
| Gln | Cys | Ala | Leu | Pro | Val | Ala | Leu | Ser | Gly | Ser | Gly | Gly | Pro | Pro | Ala |
|     |     | 35  |     |     |     |     | 40  |     |     |     |     | 45  |     |     |     |
| Leu | Asn | His | Ala | Val | Leu | Arg | Ala | Leu | Met | His | Ala | Ala | Ala | Pro | Gly |
|     | 50  |     |     |     |     | 55  |     |     |     |     | 60  |     |     |     |     |
| Ala | Ala | Asp | Leu | Pro | Cys | Cys | Val | Pro | Ala | Arg | Leu | Ser | Pro | Ile | Ser |
| 65  |     |     |     |     | 70  |     |     |     |     | 75  |     |     |     |     | 80  |
| Val | Leu | Phe | Phe | Asp | Asn | Ser | Asp | Asn | Val | Val | Leu | Arg | Gln | Tyr | Glu |
|     |     |     |     | 85  |     |     |     |     | 90  |     |     |     |     | 95  |     |
| Asp | Met | Val | Val | Asp | Glu | Cys | Gly | Cys | Arg |     |     |     |     |     |     |
|     |     |     | 100 |     |     |     |     | 105 |     |     |     |     |     |     |     |

(i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 5 amino acids  
 (B) TYPE: amino acid  
 (C) STRANDEDNESS: single  
 (D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

Cys Xaa Xaa Xaa Xaa  
1 5

(i) SEQUENCE CHARACTERISTICS:  
 (A) LENGTH: 1822 base pairs  
 (B) TYPE: nucleic acid  
 (C) STRANDEDNESS: single  
 (D) TOPOLOGY: linear

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO



|                   |                   |                   |            |                   |                   |                   |                   |                   |                   |                   |                   |                   |                   |                   |                   |      |
|-------------------|-------------------|-------------------|------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|------|
| CAC<br>His        | CCA<br>Pro        | CGC<br>Arg<br>150 | TAC<br>Tyr | CAC<br>His        | CAT<br>His        | CGA<br>Arg        | GAG<br>Glu<br>155 | TTC<br>Phe        | CGG<br>Arg        | TTT<br>Phe        | GAT<br>Asp        | CTT<br>Leu<br>160 | TCC<br>Ser        | AAG<br>Lys        | ATC<br>Ile        | 537  |
| CCA<br>Pro        | GAA<br>Glu<br>165 | GGG<br>Gly        | GAA<br>Glu | GCT<br>Ala        | GTC<br>Val        | ACG<br>Thr<br>170 | GCA<br>Ala        | GCC<br>Ala        | GAA<br>Glu        | TTC<br>Phe        | CGG<br>Arg<br>175 | ATC<br>Ile        | TAC<br>Tyr        | AAG<br>Lys        | GAC<br>Asp        | 585  |
| TAC<br>Tyr<br>180 | ATC<br>Ile        | CGG<br>Arg        | GAA<br>Glu | CGC<br>Arg        | TTC<br>Phe<br>185 | GAC<br>Asp        | AAT<br>Asn        | GAG<br>Glu        | ACG<br>Thr        | TTC<br>Phe<br>190 | CGG<br>Arg        | ATC<br>Ile        | AGC<br>Ser        | GTT<br>Val        | TAT<br>Tyr<br>195 | 633  |
| CAG<br>Gln        | GTG<br>Val        | CTC<br>Leu        | CAG<br>Gln | GAG<br>Glu<br>200 | CAC<br>His        | TTG<br>Leu        | GGC<br>Gly        | AGG<br>Arg        | GAA<br>Glu<br>205 | TCG<br>Ser        | GAT<br>Asp        | CTC<br>Leu        | TTC<br>Phe        | CTG<br>Leu<br>210 | CTC<br>Leu        | 681  |
| GAC<br>Asp        | AGC<br>Ser        | CGT<br>Arg<br>215 | ACC<br>Thr | CTC<br>Leu        | TGG<br>Trp        | GCC<br>Ala        | TCG<br>Ser<br>220 | GAG<br>Glu        | GAG<br>Glu        | GGC<br>Gly        | TGG<br>Trp        | CTG<br>Leu<br>225 | GTG<br>Val        | TTT<br>Phe        | GAC<br>Asp        | 729  |
| ATC<br>Ile        | ACA<br>Thr<br>230 | GCC<br>Ala        | ACC<br>Thr | AGC<br>Ser        | AAC<br>Asn        | CAC<br>His        | TGG<br>Trp<br>235 | GTG<br>Val        | GTC<br>Val        | AAT<br>Asn        | CCG<br>Pro        | CGG<br>Arg<br>240 | CAC<br>His        | AAC<br>Asn        | CTG<br>Leu        | 777  |
| GGC<br>Gly        | CTG<br>Leu<br>245 | CAG<br>Gln        | CTC<br>Leu | TCG<br>Ser        | GTG<br>Val        | GAG<br>Glu<br>250 | ACG<br>Thr        | CTG<br>Leu        | GAT<br>Asp        | GGG<br>Gly        | CAG<br>Gln<br>255 | AGC<br>Ser        | ATC<br>Ile        | AAC<br>Asn        | CCC<br>Pro        | 825  |
| AAG<br>Lys<br>260 | TTG<br>Leu        | GCG<br>Ala        | GGC<br>Gly | CTG<br>Leu<br>265 | ATT<br>Ile        | GGG<br>Gly        | CGG<br>Arg        | CAC<br>His        | GGG<br>Gly        | CCC<br>Pro<br>270 | CAG<br>Gln        | AAC<br>Asn        | AAG<br>Lys        | CAG<br>Gln        | CCC<br>Pro<br>275 | 873  |
| TTC<br>Phe        | ATG<br>Met        | GTG<br>Val        | GCT<br>Ala | TTC<br>Phe<br>280 | TTC<br>Phe        | AAG<br>Lys        | GCC<br>Ala        | ACG<br>Thr        | GAG<br>Glu<br>285 | GTC<br>Val        | CAC<br>His        | TTC<br>Phe        | CGC<br>Arg        | AGC<br>Ser<br>290 | ATC<br>Ile        | 921  |
| CGG<br>Arg        | TCC<br>Ser        | ACG<br>Thr<br>295 | GGG<br>Gly | AGC<br>Ser        | AAA<br>Lys        | CAG<br>Gln        | CGC<br>Arg        | AGC<br>Ser<br>300 | CAG<br>Gln        | AAC<br>Asn        | CGC<br>Arg        | TCC<br>Ser        | AAG<br>Lys<br>305 | ACG<br>Thr        | CCC<br>Pro        | 969  |
| AAG<br>Lys        | AAC<br>Asn<br>310 | CAG<br>Gln        | GAA<br>Glu | GCC<br>Ala        | CTG<br>Leu        | CGG<br>Arg        | ATG<br>Met<br>315 | GCC<br>Ala        | AAC<br>Asn        | GTG<br>Val        | GCA<br>Ala<br>320 | GAG<br>Glu<br>320 | AAC<br>Asn        | AGC<br>Ser        | AGC<br>Ser        | 1017 |
| AGC<br>Ser        | GAC<br>Asp<br>325 | CAG<br>Gln        | AGG<br>Arg | CAG<br>Gln        | GCC<br>Ala        | TGT<br>Cys<br>330 | AAG<br>Lys        | AAG<br>Lys        | CAC<br>His        | GAG<br>Glu        | CTG<br>Leu<br>335 | TAT<br>Tyr        | GTC<br>Val        | AGC<br>Ser        | TTC<br>Phe        | 1065 |
| CGA<br>Arg<br>340 | GAC<br>Asp        | CTG<br>Leu        | GGC<br>Gly | TGG<br>Trp<br>345 | CAG<br>Gln        | GAC<br>Asp        | TGG<br>Trp        | ATC<br>Ile        | ATC<br>Ile        | GCG<br>Ala<br>350 | CCT<br>Pro        | GAA<br>Glu        | GGC<br>Gly        | TAC<br>Tyr        | GCC<br>Ala<br>355 | 1113 |
| GCC<br>Ala        | TAC<br>Tyr        | TAC<br>Tyr        | TGT<br>Cys | GAG<br>Glu<br>360 | GGG<br>Gly        | GAG<br>Glu        | TGT<br>Cys        | GCC<br>Ala        | TTC<br>Phe<br>365 | CCT<br>Pro        | CTG<br>Leu        | AAC<br>Asn        | TCC<br>Ser        | TAC<br>Tyr<br>370 | ATG<br>Met        | 1161 |

|                                                                   |      |
|-------------------------------------------------------------------|------|
| AAC GCC ACC AAC CAC GCC ATC GTG CAG ACG CTG GTC CAC TTC ATC AAC   | 1209 |
| Asn Ala Thr Asn His Ala Ile Val Gln Thr Leu Val His Phe Ile Asn   |      |
| 375 380 385                                                       |      |
| CCG GAA ACG GTG CCC AAG CCC TGC TGT GCG CCC ACG CAG CTC AAT GCC   | 1257 |
| Pro Glu Thr Val Pro Lys Pro Cys Cys Ala Pro Thr Gln Leu Asn Ala   |      |
| 390 395 400                                                       |      |
| ATC TCC GTC CTC TAC TTC GAT GAC AGC TCC AAC GTC ATC CTG AAG AAA   | 1305 |
| Ile Ser Val Leu Tyr Phe Asp Asp Ser Ser Asn Val Ile Leu Lys Lys   |      |
| 405 410 415                                                       |      |
| TAC AGA AAC ATG GTG GTC CGG GCC TGT GGC TGC CAC TAGCTCCTCC        | 1351 |
| Tyr Arg Asn Met Val Val Arg Ala Cys Gly Cys His                   |      |
| 420 425 430                                                       |      |
| GAGAATTCAG ACCCTTTGGG GCCAAGTTTT TCTGGATCCT CCATTGCTCG CCTTGGCCAG | 1411 |
| GAACCAGCAG ACCAACTGCC TTTTGTGAGA CCTTCCCCTC CCTATCCCCA ACTTTAAAGG | 1471 |
| TGTGAGAGTA TTAGGAAACA TGAGCAGCAT ATGGCTTTTG ATCAGTTTTT CAGTGGCAGC | 1531 |
| ATCCAATGAA CAAGATCCTA CAAGCTGTGC AGGCAAAACC TAGCAGGAAA AAAAAACAAC | 1591 |
| GCATAAAGAA AAATGGCCGG GCCAGGTCAT TGGCTGGGAA GTCTCAGCCA TGCACGGACT | 1651 |
| CGTTTCCAGA GGTAATTATG AGCGCCTACC AGCCAGGCCA CCCAGCCGTG GGAGGAAGGG | 1711 |
| GGCGTGGCAA GGGGTGGGCA CATTGGTGTG TGTGCGAAAG GAAAATTGAC CCGGAAGTTC | 1771 |
| CTGTAATAAA TGTCACAATA AAACGAATGA ATGAAAAAAAA AAAAAAAAAA A         | 1822 |

(2) INFORMATION FOR SEQ ID NO:17:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 431 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:

|                                                                 |  |
|-----------------------------------------------------------------|--|
| Met His Val Arg Ser Leu Arg Ala Ala Ala Pro His Ser Phe Val Ala |  |
| 1 5 10 15                                                       |  |
| Leu Trp Ala Pro Leu Phe Leu Leu Arg Ser Ala Leu Ala Asp Phe Ser |  |
| 20 25 30                                                        |  |
| Leu Asp Asn Glu Val His Ser Ser Phe Ile His Arg Arg Leu Arg Ser |  |
| 35 40 45                                                        |  |
| Gln Glu Arg Arg Glu Met Gln Arg Glu Ile Leu Ser Ile Leu Gly Leu |  |
| 50 55 60                                                        |  |





Gly Tyr Ala Ala Tyr Tyr Cys Glu Gly Glu Cys Ala Phe Pro Leu Asn  
 355 360 365

Ser Tyr Met Asn Ala Thr Asn His Ala Ile Val Gln Thr Leu Val His  
 370 375 380

Phe Ile Asn Pro Glu Thr Val Pro Lys Pro Cys Cys Ala Pro Thr Gln  
 385 390 395 400

Leu Asn Ala Ile Ser Val Leu Tyr Phe Asp Asp Ser Ser Asn Val Ile  
 405 410 415

Leu Lys Lys Tyr Arg Asn Met Val Val Arg Ala Cys Gly Cys His  
 420 425 430

(2) INFORMATION FOR SEQ ID NO:18:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1873 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

(vi) ORIGINAL SOURCE:

- (A) ORGANISM: MURIDAE
- (F) TISSUE TYPE: EMBRYO

(ix) FEATURE:

- (A) NAME/KEY: CDS
- (B) LOCATION: 104..1393
- (D) OTHER INFORMATION: /function= "OSTEOGENIC PROTEIN"  
 /product= "MOP1"  
 /note= "MOP1 (CDNA)"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:

|                                                                   |     |
|-------------------------------------------------------------------|-----|
| CTGCAGCAAG TGACCTCGGG TCGTGGACCG CTGCCCTGCC CCCTCCGCTG CCACCTGGGG | 60  |
| CGGCGCGGGC CCGGTGCCCC GGATCGCGCG TAGAGCCGGC GCG ATG CAC GTG CGC   | 115 |
| Met His Val Arg                                                   |     |
| 1                                                                 |     |
| TCG CTG CGC GCT GCG GCG CCA CAC AGC TTC GTG GCG CTC TGG GCG CCT   | 163 |
| Ser Leu Arg Ala Ala Ala Pro His Ser Phe Val Ala Leu Trp Ala Pro   |     |
| 5 10 15 20                                                        |     |
| CTG TTC TTG CTG CGC TCC GCC CTG GCC GAT TTC AGC CTG GAC AAC GAG   | 211 |
| Leu Phe Leu Leu Arg Ser Ala Leu Ala Asp Phe Ser Leu Asp Asn Glu   |     |
| 25 30 35                                                          |     |

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|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| GTG | CAC | TCC | AGC | TTC | ATC | CAC | CGG | CGC | CTC | CGC | AGC | CAG | GAG | CGG | CGG | 259 |
| Val | His | Ser | Ser | Phe | Ile | His | Arg | Arg | Leu | Arg | Ser | Gln | Glu | Arg | Arg |     |
|     |     |     | 40  |     |     |     |     | 45  |     |     |     |     | 50  |     |     |     |
| GAG | ATG | CAG | CGG | GAG | ATC | CTG | TCC | ATC | TTA | GGG | TTG | CCC | CAT | CGC | CCG | 307 |
| Glu | Met | Gln | Arg | Glu | Ile | Leu | Ser | Ile | Leu | Gly | Leu | Pro | His | Arg | Pro |     |
|     |     | 55  |     |     |     |     | 60  |     |     |     |     | 65  |     |     |     |     |
| CGC | CCG | CAC | CTC | CAG | GGA | AAG | CAT | AAT | TCG | GCG | CCC | ATG | TTC | ATG | TTG | 355 |
| Arg | Pro | His | Leu | Gln | Gly | Lys | His | Asn | Ser | Ala | Pro | Met | Phe | Met | Leu |     |
|     | 70  |     |     |     |     | 75  |     |     |     |     | 80  |     |     |     |     |     |
| GAC | CTG | TAC | AAC | GCC | ATG | GCG | GTG | GAG | GAG | AGC | GGG | CCG | GAC | GGA | CAG | 403 |
| Asp | Leu | Tyr | Asn | Ala | Met | Ala | Val | Glu | Glu | Ser | Gly | Pro | Asp | Gly | Gln |     |
|     | 85  |     |     |     | 90  |     |     |     |     | 95  |     |     |     |     | 100 |     |
| GGC | TTC | TCC | TAC | CCC | TAC | AAG | GCC | GTC | TTC | AGT | ACC | CAG | GGC | CCC | CCT | 451 |
| Gly | Phe | Ser | Tyr | Pro | Tyr | Lys | Ala | Val | Phe | Ser | Thr | Gln | Gly | Pro | Pro |     |
|     |     |     |     | 105 |     |     |     |     | 110 |     |     |     |     | 115 |     |     |
| TTA | GCC | AGC | CTG | CAG | GAC | AGC | CAT | TTC | CTC | ACT | GAC | GCC | GAC | ATG | GTC | 499 |
| Leu | Ala | Ser | Leu | Gln | Asp | Ser | His | Phe | Leu | Thr | Asp | Ala | Asp | Met | Val |     |
|     |     |     | 120 |     |     |     |     | 125 |     |     |     |     | 130 |     |     |     |
| ATG | AGC | TTC | GTC | AAC | CTA | GTG | GAA | CAT | GAC | AAA | GAA | TTC | TTC | CAC | CCT | 547 |
| Met | Ser | Phe | Val | Asn | Leu | Val | Glu | His | Asp | Lys | Glu | Phe | Phe | His | Pro |     |
|     |     | 135 |     |     |     |     | 140 |     |     |     |     | 145 |     |     |     |     |
| CGA | TAC | CAC | CAT | CGG | GAG | TTC | CGG | TTT | GAT | CTT | TCC | AAG | ATC | CCC | GAG | 595 |
| Arg | Tyr | His | His | Arg | Glu | Phe | Arg | Phe | Asp | Leu | Ser | Lys | Ile | Pro | Glu |     |
|     | 150 |     |     |     |     | 155 |     |     |     |     | 160 |     |     |     |     |     |
| GGC | GAA | CGG | GTG | ACC | GCA | GCC | GAA | TTC | AGG | ATC | TAT | AAG | GAC | TAC | ATC | 643 |
| Gly | Glu | Arg | Val | Thr | Ala | Ala | Glu | Phe | Arg | Ile | Tyr | Lys | Asp | Tyr | Ile |     |
|     | 165 |     |     |     | 170 |     |     |     |     | 175 |     |     |     |     | 180 |     |
| CGG | GAG | CGA | TTT | GAC | AAC | GAG | ACC | TTC | CAG | ATC | ACA | GTC | TAT | CAG | GTG | 691 |
| Arg | Glu | Arg | Phe | Asp | Asn | Glu | Thr | Phe | Gln | Ile | Thr | Val | Tyr | Gln | Val |     |
|     |     |     |     | 185 |     |     |     |     | 190 |     |     |     |     | 195 |     |     |
| CTC | CAG | GAG | CAC | TCA | GGC | AGG | GAG | TCG | GAC | CTC | TTC | TTG | CTG | GAC | AGC | 739 |
| Leu | Gln | Glu | His | Ser | Gly | Arg | Glu | Ser | Asp | Leu | Phe | Leu | Leu | Asp | Ser |     |
|     |     |     | 200 |     |     |     |     | 205 |     |     |     |     | 210 |     |     |     |
| CGC | ACC | ATC | TGG | GCT | TCT | GAG | GAG | GGC | TGG | TTG | GTG | TTT | GAT | ATC | ACA | 787 |
| Arg | Thr | Ile | Trp | Ala | Ser | Glu | Glu | Gly | Trp | Leu | Val | Phe | Asp | Ile | Thr |     |
|     |     | 215 |     |     |     |     | 220 |     |     |     |     | 225 |     |     |     |     |
| GCC | ACC | AGC | AAC | CAC | TGG | GTG | GTC | AAC | CCT | CGG | CAC | AAC | CTG | GGC | TTA | 835 |
| Ala | Thr | Ser | Asn | His | Trp | Val | Val | Asn | Pro | Arg | His | Asn | Leu | Gly | Leu |     |
|     | 230 |     |     |     |     | 235 |     |     |     |     | 240 |     |     |     |     |     |
| CAG | CTC | TCT | GTG | GAG | ACC | CTG | GAT | GGG | CAG | AGC | ATC | AAC | CCC | AAG | TTG | 883 |
| Gln | Leu | Ser | Val | Glu | Thr | Leu | Asp | Gly | Gln | Ser | Ile | Asn | Pro | Lys | Leu |     |
|     | 245 |     |     |     | 250 |     |     |     |     | 255 |     |     |     |     | 260 |     |

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(2) INFORMATION FOR SEQ ID NO:19:

(A) LENGTH: 430 amino acids

(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:

Val Tyr Gln Val Leu Gln Glu His Ser Gly Arg Glu Ser Asp Leu Phe  
195 200 205

Leu Leu Asp Ser Arg Thr Ile Trp Ala Ser Glu Glu Gly Trp Leu Val  
 210 215 220

Phe Asp Ile Thr Ala Thr Ser Asn His Trp Val Val Asn Pro Arg His  
 225 230 235 240

Asn Leu Gly Leu Gln Leu Ser Val Glu Thr Leu Asp Gly Gln Ser Ile  
 245 250 255

Asn Pro Lys Leu Ala Gly Leu Ile Gly Arg His Gly Pro Gln Asn Lys  
 260 265 270

Gln Pro Phe Met Val Ala Phe Phe Lys Ala Thr Glu Val His Leu Arg  
 275 280 285

Ser Ile Arg Ser Thr Gly Gly Lys Gln Arg Ser Gln Asn Arg Ser Lys  
 290 295 300

Thr Pro Lys Asn Gln Glu Ala Leu Arg Met Ala Ser Val Ala Glu Asn  
 305 310 315 320

Ser Ser Ser Asp Gln Arg Gln Ala Cys Lys Lys His Glu Leu Tyr Val  
 325 330 335

Ser Phe Arg Asp Leu Gly Trp Gln Asp Trp Ile Ile Ala Pro Glu Gly  
 340 345 350

Tyr Ala Ala Tyr Tyr Cys Glu Gly Glu Cys Ala Phe Pro Leu Asn Ser  
 355 360 365

Tyr Met Asn Ala Thr Asn His Ala Ile Val Gln Thr Leu Val His Phe  
 370 375 380

Ile Asn Pro Asp Thr Val Pro Lys Pro Cys Cys Ala Pro Thr Gln Leu  
 385 390 395 400

Asn Ala Ile Ser Val Leu Tyr Phe Asp Asp Ser Ser Asn Val Asp Leu  
 405 410 415

Lys Lys Tyr Arg Asn Met Val Val Arg Ala Cys Gly Cys His  
 420 425 430

(2) INFORMATION FOR SEQ ID NO:20:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1723 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(vi) ORIGINAL SOURCE:

- (A) ORGANISM: Homo sapiens
- (F) TISSUE TYPE: HIPPOCAMPUS

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|                                                                                                                                                       |      |
|-------------------------------------------------------------------------------------------------------------------------------------------------------|------|
| AAC ATG GTG GAG CGA GAC CGT GCC CTG GGC CAC CAG GAG CCC CAT TGG<br>Asn Met Val Glu Arg Asp Arg Ala Leu Gly His Gln Glu Pro His Trp<br>110 115 120 125 | 864  |
| AAG GAG TTC CGC TTT GAC CTG ACC CAG ATC CCG GCT GGG GAG GCG GTC<br>Lys Glu Phe Arg Phe Asp Leu Thr Gln Ile Pro Ala Gly Glu Ala Val<br>130 135 140     | 912  |
| ACA GCT GCG GAG TTC CGG ATT TAC AAG GTG CCC AGC ATC CAC CTG CTC<br>Thr Ala Ala Glu Phe Arg Ile Tyr Lys Val Pro Ser Ile His Leu Leu<br>145 150 155     | 960  |
| AAC AGG ACC CTC CAC GTC AGC ATG TTC CAG GTG GTC CAG GAG CAG TCC<br>Asn Arg Thr Leu His Val Ser Met Phe Gln Val Val Gln Glu Gln Ser<br>160 165 170     | 1008 |
| AAC AGG GAG TCT GAC TTG TTC TTT TTG GAT CTT CAG ACG CTC CGA GCT<br>Asn Arg Glu Ser Asp Leu Phe Phe Leu Asp Leu Gln Thr Leu Arg Ala<br>175 180 185     | 1056 |
| GGA GAC GAG GGC TGG CTG GTG CTG GAT GTC ACA GCA GCC AGT GAC TGC<br>Gly Asp Glu Gly Trp Leu Val Leu Asp Val Thr Ala Ala Ser Asp Cys<br>190 195 200 205 | 1104 |
| TGG TTG CTG AAG CGT CAC AAG GAC CTG GGA CTC CGC CTC TAT GTG GAG<br>Trp Leu Leu Lys Arg His Lys Asp Leu Gly Leu Arg Leu Tyr Val Glu<br>210 215 220     | 1152 |
| ACT GAG GAC GGG CAC AGC GTG GAT CCT GGC CTG GCC GGC CTG CTG GGT<br>Thr Glu Asp Gly His Ser Val Asp Pro Gly Leu Ala Gly Leu Leu Gly<br>225 230 235     | 1200 |
| CAA CGG GCC CCA CGC TCC CAA CAG CCT TTC GTG GTC ACT TTC TTC AGG<br>Gln Arg Ala Pro Arg Ser Gln Gln Pro Phe Val Val Thr Phe Phe Arg<br>240 245 250     | 1248 |
| GCC AGT CCG AGT CCC ATC CGC ACC CCT CGG GCA GTG AGG CCA CTG AGG<br>Ala Ser Pro Ser Pro Ile Arg Thr Pro Arg Ala Val Arg Pro Leu Arg<br>255 260 265     | 1296 |
| AGG AGG CAG CCG AAG AAA AGC AAC GAG CTG CCG CAG GCC AAC CGA CTC<br>Arg Arg Gln Pro Lys Lys Ser Asn Glu Leu Pro Gln Ala Asn Arg Leu<br>270 275 280 285 | 1344 |
| CCA GGG ATC TTT GAT GAC GTC CAC GGC TCC CAC GGC CGG CAG GTC TGC<br>Pro Gly Ile Phe Asp Asp Val His Gly Ser His Gly Arg Gln Val Cys<br>290 295 300     | 1392 |
| CGT CGG CAC GAG CTC TAC GTC AGC TTC CAG GAC CTC GGC TGG CTG GAC<br>Arg Arg His Glu Leu Tyr Val Ser Phe Gln Asp Leu Gly Trp Leu Asp<br>305 310 315     | 1440 |
| TGG GTC ATC GCT CCC CAA GGC TAC TCG GCC TAT TAC TGT GAG GGG GAG<br>Trp Val Ile Ala Pro Gln Gly Tyr Ser Ala Tyr Tyr Cys Glu Gly Glu<br>320 325 330     | 1488 |

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|                                                                 |      |
|-----------------------------------------------------------------|------|
| TGC TCC TTC CCA CTG GAC TCC TGC ATG AAT GCC ACC AAC CAC GCC ATC | 1536 |
| Cys Ser Phe Pro Leu Asp Ser Cys Met Asn Ala Thr Asn His Ala Ile |      |
| 335 340 345                                                     |      |
| CTG CAG TCC CTG GTG CAC CTG ATG AAG CCA AAC GCA GTC CCC AAG GCG | 1584 |
| Leu Gln Ser Leu Val His Leu Met Lys Pro Asn Ala Val Pro Lys Ala |      |
| 350 355 360 365                                                 |      |
| TGC TGT GCA CCC ACC AAG CTG AGC GCC ACC TCT GTG CTC TAC TAT GAC | 1632 |
| Cys Cys Ala Pro Thr Lys Leu Ser Ala Thr Ser Val Leu Tyr Tyr Asp |      |
| 370 375 380                                                     |      |
| AGC AGC AAC AAC GTC ATC CTG CGC AAA GCC CGC AAC ATG GTG GTC AAG | 1680 |
| Ser Ser Asn Asn Val Ile Leu Arg Lys Ala Arg Asn Met Val Val Lys |      |
| 385 390 395                                                     |      |
| GCC TGC GGC TGC CAC T GAGTCAGCCC GCCCAGCCCT ACTGCAG             | 1723 |
| Ala Cys Gly Cys His                                             |      |
| 400                                                             |      |

(2) INFORMATION FOR SEQ ID NO:21:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 402 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:

|                                                                 |  |
|-----------------------------------------------------------------|--|
| Met Thr Ala Leu Pro Gly Pro Leu Trp Leu Leu Gly Leu Ala Leu Cys |  |
| 1 5 10 15                                                       |  |
| Ala Leu Gly Gly Gly Gly Pro Gly Leu Arg Pro Pro Pro Gly Cys Pro |  |
| 20 25 30                                                        |  |
| Gln Arg Arg Leu Gly Ala Arg Glu Arg Arg Asp Val Gln Arg Glu Ile |  |
| 35 40 45                                                        |  |
| Leu Ala Val Leu Gly Leu Pro Gly Arg Pro Arg Pro Arg Ala Pro Pro |  |
| 50 55 60                                                        |  |
| Ala Ala Ser Arg Leu Pro Ala Ser Ala Pro Leu Phe Met Leu Asp Leu |  |
| 65 70 75 80                                                     |  |
| Tyr His Ala Met Ala Gly Asp Asp Asp Glu Asp Gly Ala Pro Ala Glu |  |
| 85 90 95                                                        |  |
| Arg Arg Leu Gly Arg Ala Asp Leu Val Met Ser Phe Val Asn Met Val |  |
| 100 105 110                                                     |  |
| Glu Arg Asp Arg Ala Leu Gly His Gln Glu Pro His Trp Lys Glu Phe |  |
| 115 120 125                                                     |  |

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[illegible]

(2) INFORMATION FOR SEQ ID NO:22:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1926 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(vi) ORIGINAL SOURCE:

- (A) ORGANISM: MURIDAE
- (F) TISSUE TYPE: EMBRYO

(ix) FEATURE:

- (A) NAME/KEY: CDS
- (B) LOCATION: 93..1289
- (D) OTHER INFORMATION: /function= "OSTEOGENIC PROTEIN"  
/product= "mOP2-PP"  
/note= "mOP2 cDNA"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:

|                                                                   |     |
|-------------------------------------------------------------------|-----|
| GCCAGGCACA GGTGCGCCGT CTGGTCCTCC CCGTCTGGCG TCAGCCGAGC CCGACCAGCT | 60  |
| ACCAGTGGAT GCGCGCCGGC TGAAAGTCCG AG ATG GCT ATG CGT CCC GGG CCA   | 113 |
| Met Ala Met Arg Pro Gly Pro                                       |     |
| 1 5                                                               |     |
| CTC TGG CTA TTG GGC CTT GCT CTG TGC GCG CTG GGA GGC GGC CAC GGT   | 161 |
| Leu Trp Leu Leu Gly Leu Ala Leu Cys Ala Leu Gly Gly Gly His Gly   |     |
| 10 15 20                                                          |     |
| CCG CGT CCC CCG CAC ACC TGT CCC CAG CGT CGC CTG GGA GCG CGC GAG   | 209 |
| Pro Arg Pro Pro His Thr Cys Pro Gln Arg Arg Leu Gly Ala Arg Glu   |     |
| 25 30 35                                                          |     |
| CGC CGC GAC ATG CAG CGT GAA ATC CTG GCG GTG CTC GGG CTA CCG GGA   | 257 |
| Arg Arg Asp Met Gln Arg Glu Ile Leu Ala Val Leu Gly Leu Pro Gly   |     |
| 40 45 50 55                                                       |     |
| CGG CCC CGA CCC CGT GCA CAA CCC GCC GCT GCC CGG CAG CCA GCG TCC   | 305 |
| Arg Pro Arg Pro Arg Ala Gln Pro Ala Ala Arg Gln Pro Ala Ser       |     |
| 60 65 70                                                          |     |
| GCG CCC CTC TTC ATG TTG GAC CTA TAC CAC GCC ATG ACC GAT GAC GAC   | 353 |
| Ala Pro Leu Phe Met Leu Asp Leu Tyr His Ala Met Thr Asp Asp Asp   |     |
| 75 80 85                                                          |     |
| GAC GGC GGG CCA CCA CAG GCT CAC TTA GGC CGT GCC GAC CTG GTC ATG   | 401 |
| Asp Gly Gly Pro Pro Gln Ala His Leu Gly Arg Ala Asp Leu Val Met   |     |
| 90 95 100                                                         |     |
| AGC TTC GTC AAC ATG GTG GAA CGC GAC CGT ACC CTG GGC TAC CAG GAG   | 449 |
| Ser Phe Val Asn Met Val Glu Arg Asp Arg Thr Leu Gly Tyr Gln Glu   |     |
| 105 110 115                                                       |     |

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|                   |                   |                   |                   |                   |                   |                   |                   |                   |                   |                   |                   |                   |                   |                   |                   |      |
|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|------|
| CCA<br>Pro<br>120 | CAC<br>His        | TGG<br>Trp        | AAG<br>Lys        | GAA<br>Glu        | TTC<br>Phe<br>125 | CAC<br>His        | TTT<br>Phe        | GAC<br>Asp        | CTA<br>Leu        | ACC<br>Thr<br>130 | CAG<br>Gln        | ATC<br>Ile        | CCT<br>Pro        | GCT<br>Ala        | GGG<br>Gly<br>135 | 497  |
| GAG<br>Glu        | GCT<br>Ala        | GTC<br>Val        | ACA<br>Thr<br>140 | GCT<br>Ala        | GCT<br>Ala        | GAG<br>Glu        | TTC<br>Phe        | CGG<br>Arg        | ATC<br>Ile<br>145 | TAC<br>Tyr        | AAA<br>Lys        | GAA<br>Glu        | CCC<br>Pro        | AGC<br>Ser<br>150 | ACC<br>Thr        | 545  |
| CAC<br>His        | CCG<br>Pro        | CTC<br>Leu        | AAC<br>Asn<br>155 | ACA<br>Thr        | ACC<br>Thr        | CTC<br>Leu        | CAC<br>His        | ATC<br>Ile<br>160 | AGC<br>Ser        | ATG<br>Met        | TTC<br>Phe        | GAA<br>Glu        | GTG<br>Val<br>165 | GTC<br>Val        | CAA<br>Gln        | 593  |
| GAG<br>Glu        | CAC<br>His        | TCC<br>Ser<br>170 | AAC<br>Asn        | AGG<br>Arg        | GAG<br>Glu        | TCT<br>Ser        | GAC<br>Asp<br>175 | TTG<br>Leu        | TTC<br>Phe        | TTT<br>Phe        | TTG<br>Leu        | GAT<br>Asp<br>180 | CTT<br>Leu        | CAG<br>Gln        | ACG<br>Thr        | 641  |
| CTC<br>Leu        | CGA<br>Arg<br>185 | TCT<br>Ser        | GGG<br>Gly        | GAC<br>Asp        | GAG<br>Glu        | GGC<br>Gly<br>190 | TGG<br>Trp        | CTG<br>Leu        | GTG<br>Val        | CTG<br>Leu        | GAC<br>Asp<br>195 | ATC<br>Ile        | ACA<br>Thr        | GCA<br>Ala        | GCC<br>Ala        | 689  |
| AGT<br>Ser<br>200 | GAC<br>Asp        | CGA<br>Arg        | TGG<br>Trp        | CTG<br>Leu<br>205 | CTG<br>Leu        | AAC<br>Asn        | CAT<br>His        | CAC<br>His        | AAG<br>Lys        | GAC<br>Asp<br>210 | CTG<br>Leu        | GGA<br>Gly        | CTC<br>Leu        | CGC<br>Arg        | CTC<br>Leu<br>215 | 737  |
| TAT<br>Tyr        | GTG<br>Val        | GAA<br>Glu        | ACC<br>Thr<br>220 | GCG<br>Ala        | GAT<br>Asp        | GGG<br>Gly        | CAC<br>His        | AGC<br>Ser        | ATG<br>Met<br>225 | GAT<br>Asp        | CCT<br>Pro        | GGC<br>Gly        | CTG<br>Leu        | GCT<br>Ala<br>230 | GGT<br>Gly        | 785  |
| CTG<br>Leu        | CTT<br>Leu        | GGA<br>Gly        | CGA<br>Arg<br>235 | CAA<br>Gln        | GCA<br>Ala        | CCA<br>Pro        | CGC<br>Arg        | TCC<br>Ser<br>240 | AGA<br>Arg        | CAG<br>Gln        | CCT<br>Pro        | TTC<br>Phe        | ATG<br>Met<br>245 | GTA<br>Val        | ACC<br>Thr        | 833  |
| TTC<br>Phe        | TTC<br>Phe        | AGG<br>Arg<br>250 | GCC<br>Ala        | AGC<br>Ser        | CAG<br>Gln        | AGT<br>Ser        | CCT<br>Pro<br>255 | GTG<br>Val        | CGG<br>Arg        | GCC<br>Ala        | CCT<br>Pro        | CGG<br>Arg<br>260 | GCA<br>Ala        | GCG<br>Ala        | AGA<br>Arg        | 881  |
| CCA<br>Pro<br>265 | CTG<br>Leu        | AAG<br>Lys        | AGG<br>Arg        | ACG<br>Arg        | CAG<br>Gln        | CCA<br>Pro<br>270 | AAG<br>Lys        | AAA<br>Lys        | ACG<br>Thr        | AAC<br>Asn        | GAG<br>Glu<br>275 | CTT<br>Leu        | CCG<br>Pro        | CAC<br>His        | CCC<br>Pro        | 929  |
| AAC<br>Asn<br>280 | AAA<br>Lys        | CTC<br>Leu        | CCA<br>Pro        | GGG<br>Gly        | ATC<br>Ile<br>285 | TTT<br>Phe        | GAT<br>Asp        | GAT<br>Asp        | GGC<br>Gly        | CAC<br>His<br>290 | GGT<br>Gly        | TCC<br>Ser        | CGC<br>Arg        | GGC<br>Gly        | AGA<br>Arg<br>295 | 977  |
| GAG<br>Glu        | GTT<br>Val        | TGC<br>Cys        | CGC<br>Arg        | AGG<br>Arg<br>300 | CAT<br>His        | GAG<br>Glu        | CTC<br>Leu        | TAC<br>Tyr        | GTC<br>Val<br>305 | AGC<br>Ser        | TTC<br>Phe        | CGT<br>Arg        | GAC<br>Asp        | CTT<br>Leu<br>310 | GGC<br>Gly        | 1025 |
| TGG<br>Trp        | CTG<br>Leu        | GAC<br>Asp        | TGG<br>Trp<br>315 | GTC<br>Val        | ATC<br>Ile        | GCC<br>Ala        | CCC<br>Pro        | CAG<br>Gln<br>320 | GGC<br>Gly        | TAC<br>Tyr        | TCT<br>Ser        | GCC<br>Ala        | TAT<br>Tyr<br>325 | TAC<br>Tyr        | TGT<br>Cys        | 1073 |
| GAG<br>Glu        | GGG<br>Gly        | GAG<br>Glu<br>330 | TGT<br>Cys        | GCT<br>Ala        | TTC<br>Phe        | CCA<br>Pro        | CTG<br>Leu<br>335 | GAC<br>Asp        | TCC<br>Ser        | TGT<br>Cys        | ATG<br>Met        | AAC<br>Asn<br>340 | GCC<br>Ala        | ACC<br>Thr        | AAC<br>Asn        | 1121 |

|                                                                   |      |
|-------------------------------------------------------------------|------|
| CAT GCC ATC TTG CAG TCT CTG GTG CAC CTG ATG AAG CCA GAT GTT GTC   | 1169 |
| His Ala Ile Leu Gln Ser Leu Val His Leu Met Lys Pro Asp Val Val   |      |
| 345 350 355                                                       |      |
| CCC AAG GCA TGC TGT GCA CCC ACC AAA CTG AGT GCC ACC TCT GTG CTG   | 1217 |
| Pro Lys Ala Cys Cys Ala Pro Thr Lys Leu Ser Ala Thr Ser Val Leu   |      |
| 360 365 370 375                                                   |      |
| TAC TAT GAC AGC AGC AAC AAT GTC ATC CTG CGT AAA CAC CGT AAC ATG   | 1265 |
| Tyr Tyr Asp Ser Ser Asn Asn Val Ile Leu Arg Lys His Arg Asn Met   |      |
| 380 385 390                                                       |      |
| GTG GTC AAG GCC TGT GGC TGC CAC TGAGGCCCG CCCAGCATCC TGCTTCTACT   | 1319 |
| Val Val Lys Ala Cys Gly Cys His                                   |      |
| 395                                                               |      |
| ACCTTACCAT CTGGCCGGGC CCCTCTCCAG AGGCAGAAAC CCTTCTATGT TATCATAGCT | 1379 |
| CAGACAGGGG CAATGGGAGG CCCTTCACTT CCCCTGGCCA CTTCTGCTA AAATTCTGGT  | 1439 |
| CTTTCCCAGT TCCTCTGTCC TTCATGGGGT TTCGGGGCTA TCACCCCGCC CTCTCCATCC | 1499 |
| TCCTACCCCA AGCATAGACT GAATGCACAC AGCATCCCAG AGCTATGCTA ACTGAGAGGT | 1559 |
| CTGGGGTCAG CACTGAAGGC CCACATGAGG AAGACTGATC CTTGGCCATC CTCAGCCCAC | 1619 |
| AATGGCAAAT TCTGGATGGT CTAAGAAGGC CCTGGAATTC TAAACTAGAT GATCTGGGCT | 1679 |
| CTCTGCACCA TTCATTGTGG CAGTTGGGAC ATTTTGTAGGT ATAACAGACA CATACTTA  | 1739 |
| GATCAATGCA TCGCTGTACT CCTTGAAATC AGAGCTAGCT TGTTAGAAAA AGAATCAGAG | 1799 |
| CCAGGTATAG CGGTGCATGT CATTAATCCC AGCGCTAAAG AGACAGAGAC AGGAGAATCT | 1859 |
| CTGTGAGTTC AAGGCCACAT AGAAAGAGCC TGTCTCGGGA GCAGGAAAAA AAAAAAAAC  | 1919 |
| GGAATTC                                                           | 1926 |

(2) INFORMATION FOR SEQ ID NO:23:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 399 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Met | Ala | Met | Arg | Pro | Gly | Pro | Leu | Trp | Leu | Leu | Gly | Leu | Ala | Leu | Cys |
| 1   |     |     |     | 5   |     |     |     | 10  |     |     |     |     |     | 15  |     |
| Ala | Leu | Gly | Gly | Gly | His | Gly | Pro | Arg | Pro | Pro | His | Thr | Cys | Pro | Gln |
|     |     | 20  |     |     |     |     |     | 25  |     |     |     |     | 30  |     |     |

Arg Arg Leu Gly Ala Arg Glu Arg Arg Asp Met Gln Arg Glu Ile Leu  
35 40 45

Ala Val Leu Gly Leu Pro Gly Arg Pro Arg Pro Arg Ala Gln Pro Ala  
50 55 60

Ala Ala Arg Gln Pro Ala Ser Ala Pro Leu Phe Met Leu Asp Leu Tyr  
65 70 75 80

His Ala Met Thr Asp Asp Asp Asp Gly Gly Pro Pro Gln Ala His Leu  
85 90 95

Gly Arg Ala Asp Leu Val Met Ser Phe Val Asn Met Val Glu Arg Asp  
100 105 110

Arg Thr Leu Gly Tyr Gln Glu Pro His Trp Lys Glu Phe His Phe Asp  
115 120 125

Leu Thr Gln Ile Pro Ala Gly Glu Ala Val Thr Ala Ala Glu Phe Arg  
130 135 140

Ile Tyr Lys Glu Pro Ser Thr His Pro Leu Asn Thr Thr Leu His Ile  
145 150 155 160

Ser Met Phe Glu Val Val Gln Glu His Ser Asn Arg Glu Ser Asp Leu  
165 170 175

Phe Phe Leu Asp Leu Gln Thr Leu Arg Ser Gly Asp Glu Gly Trp Leu  
180 185 190

Val Leu Asp Ile Thr Ala Ala Ser Asp Arg Trp Leu Leu Asn His His  
195 200 205

Lys Asp Leu Gly Leu Arg Leu Tyr Val Glu Thr Ala Asp Gly His Ser  
210 215 220

Met Asp Pro Gly Leu Ala Gly Leu Leu Gly Arg Gln Ala Pro Arg Ser  
225 230 235 240

Arg Gln Pro Phe Met Val Thr Phe Phe Arg Ala Ser Gln Ser Pro Val  
245 250 255

Arg Ala Pro Arg Ala Ala Arg Pro Leu Lys Arg Arg Gln Pro Lys Lys  
260 265 270

Thr Asn Glu Leu Pro His Pro Asn Lys Leu Pro Gly Ile Phe Asp Asp  
275 280 285

Gly His Gly Ser Arg Gly Arg Glu Val Cys Arg Arg His Glu Leu Tyr  
290 295 300

Val Ser Phe Arg Asp Leu Gly Trp Leu Asp Trp Val Ile Ala Pro Gln  
305 310 315 320

Gly Tyr Ser Ala Tyr Tyr Cys Glu Gly Glu Cys Ala Phe Pro Leu Asp  
325 330 335

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Ser Cys Met Asn Ala Thr Asn His Ala Ile Leu Gln Ser Leu Val His  
 340 345 350

Leu Met Lys Pro Asp Val Val Pro Lys Ala Cys Cys Ala Pro Thr Lys  
 355 360 365

Leu Ser Ala Thr Ser Val Leu Tyr Tyr Asp Ser Ser Asn Asn Val Ile  
 370 375 380

Leu Arg Lys His Arg Asn Met Val Val Lys Ala Cys Gly Cys His  
 385 390 395

(2) INFORMATION FOR SEQ ID NO:24:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1368 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:

- (A) NAME/KEY: CDS
- (B) LOCATION: 1..1368

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:

|                                                                 |     |
|-----------------------------------------------------------------|-----|
| ATG TCG GGA CTG CGA AAC ACC TCG GAG GCC GTT GCA GTG CTC GCC TCC | 48  |
| Met Ser Gly Leu Arg Asn Thr Ser Glu Ala Val Ala Val Leu Ala Ser |     |
| 1 5 10 15                                                       |     |
| CTG GGA CTC GGA ATG GTT CTG CTC ATG TTC GTG GCG ACC ACG CCG CCG | 96  |
| Leu Gly Leu Gly Met Val Leu Leu Met Phe Val Ala Thr Thr Pro Pro |     |
| 20 25 30                                                        |     |
| GCC GTT GAG GCC ACC CAG TCG GGG ATT TAC ATA GAC AAC GGC AAG GAC | 144 |
| Ala Val Glu Ala Thr Gln Ser Gly Ile Tyr Ile Asp Asn Gly Lys Asp |     |
| 35 40 45                                                        |     |
| CAG ACG ATC ATG CAC AGA GTG CTG AGC GAG GAC GAC AAG CTG GAC GTC | 192 |
| Gln Thr Ile Met His Arg Val Leu Ser Glu Asp Asp Lys Leu Asp Val |     |
| 50 55 60                                                        |     |
| TCG TAC GAG ATC CTC GAG TTC CTG GGC ATC GCC GAA CGG CCG ACG CAC | 240 |
| Ser Tyr Glu Ile Leu Glu Phe Leu Gly Ile Ala Glu Arg Pro Thr His |     |
| 65 70 75 80                                                     |     |
| CTG AGC AGC CAC CAG TTG TCG CTG AGG AAG TCG GCT CCC AAG TTC CTG | 288 |
| Leu Ser Ser His Gln Leu Ser Leu Arg Lys Ser Ala Pro Lys Phe Leu |     |
| 85 90 95                                                        |     |

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110 09

|                                                                 |      |
|-----------------------------------------------------------------|------|
| CAC AGG AGC AAG CGA AGC GCC AGC CAT CCA CGC AAG CGC AAG AAG TCG | 1008 |
| His Arg Ser Lys Arg Ser Ala Ser His Pro Arg Lys Arg Lys Lys Ser |      |
| 325 330 335                                                     |      |
| GTG TCG CCC AAC AAC GTG CCG CTG CTG GAA CCG ATG GAG AGC ACG CGC | 1056 |
| Val Ser Pro Asn Asn Val Pro Leu Leu Glu Pro Met Glu Ser Thr Arg |      |
| 340 345 350                                                     |      |
| AGC TGC CAG ATG CAG ACC CTG TAC ATA GAC TTC AAG GAT CTG GGC TGG | 1104 |
| Ser Cys Gln Met Gln Thr Leu Tyr Ile Asp Phe Lys Asp Leu Gly Trp |      |
| 355 360 365                                                     |      |
| CAT GAC TGG ATC ATC GCA CCA GAG GGC TAT GGC GCC TTC TAC TGC AGC | 1152 |
| His Asp Trp Ile Ile Ala Pro Glu Gly Tyr Gly Ala Phe Tyr Cys Ser |      |
| 370 375 380                                                     |      |
| GGC GAG TGC AAT TTC CCG CTC AAT GCG CAC ATG AAC GCC ACG AAC CAT | 1200 |
| Gly Glu Cys Asn Phe Pro Leu Asn Ala His Met Asn Ala Thr Asn His |      |
| 385 390 395 400                                                 |      |
| GCG ATC GTC CAG ACC CTG GTC CAC CTG CTG GAG CCC AAG AAG GTG CCC | 1248 |
| Ala Ile Val Gln Thr Leu Val His Leu Leu Glu Pro Lys Lys Val Pro |      |
| 405 410 415                                                     |      |
| AAG CCC TGC TGC GCT CCG ACC AGG CTG GGA GCA CTA CCC GTT CTG TAC | 1296 |
| Lys Pro Cys Cys Ala Pro Thr Arg Leu Gly Ala Leu Pro Val Leu Tyr |      |
| 420 425 430                                                     |      |
| CAC CTG AAC GAC GAG AAT GTG AAC CTG AAA AAG TAT AGA AAC ATG ATT | 1344 |
| His Leu Asn Asp Glu Asn Val Asn Leu Lys Lys Tyr Arg Asn Met Ile |      |
| 435 440 445                                                     |      |
| GTG AAA TCC TGC GCG TGC CAT TGA                                 | 1368 |
| Val Lys Ser Cys Gly Cys His                                     |      |
| 450 455                                                         |      |

(2) INFORMATION FOR SEQ ID NO:25:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 455 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:25:

|                                                                 |
|-----------------------------------------------------------------|
| Met Ser Gly Leu Arg Asn Thr Ser Glu Ala Val Ala Val Leu Ala Ser |
| 1 5 10 15                                                       |
| Leu Gly Leu Gly Met Val Leu Leu Met Phe Val Ala Thr Thr Pro Pro |
| 20 25 30                                                        |



Ala Val Glu Ala Thr Gln Ser Gly Ile Tyr Ile Asp Asn Gly Lys Asp  
35 40 45

Gln Thr Ile Met His Arg Val Leu Ser Glu Asp Asp Lys Leu Asp Val  
50 55 60

Ser Tyr Glu Ile Leu Glu Phe Leu Gly Ile Ala Glu Arg Pro Thr His  
65 70 75 80

Leu Ser Ser His Gln Leu Ser Leu Arg Lys Ser Ala Pro Lys Phe Leu  
85 90 95

Leu Asp Val Tyr His Arg Ile Thr Ala Glu Glu Gly Leu Ser Asp Gln  
100 105 110

Asp Glu Asp Asp Asp Tyr Glu Arg Gly His Arg Ser Arg Arg Ser Ala  
115 120 125

Asp Leu Glu Glu Asp Glu Gly Glu Gln Gln Lys Asn Phe Ile Thr Asp  
130 135 140

Leu Asp Lys Arg Ala Ile Asp Glu Ser Asp Ile Ile Met Thr Phe Leu  
145 150 155 160

Asn Lys Arg His His Asn Val Asp Glu Leu Arg His Glu His Gly Arg  
165 170 175

Arg Leu Trp Phe Asp Val Ser Asn Val Pro Asn Asp Asn Tyr Leu Val  
180 185 190

Met Ala Glu Leu Arg Ile Tyr Gln Asn Ala Asn Glu Gly Lys Trp Leu  
195 200 205

Thr Ala Asn Arg Glu Phe Thr Ile Thr Val Tyr Ala Ile Gly Thr Gly  
210 215 220

Thr Leu Gly Gln His Thr Met Glu Pro Leu Ser Ser Val Asn Thr Thr  
225 230 235 240

Gly Asp Tyr Val Gly Trp Leu Glu Leu Asn Val Thr Glu Gly Leu His  
245 250 255

Glu Trp Leu Val Lys Ser Lys Asp Asn His Gly Ile Tyr Ile Gly Ala  
260 265 270

His Ala Val Asn Arg Pro Asp Arg Glu Val Lys Leu Asp Asp Ile Gly  
275 280 285

Leu Ile His Arg Lys Val Asp Asp Glu Phe Gln Pro Phe Met Ile Gly  
290 295 300

Phe Phe Arg Gly Pro Glu Leu Ile Lys Ala Thr Ala His Ser Ser His  
305 310 315 320

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(2) INFORMATION FOR SEQ ID NO:26:

(A) LENGTH: 104 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

(ix) FEATURE:

- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:26:

Cys Ala Arg Arg Tyr Leu Lys Val Asp Phe Ala Asp Ile Gly Trp Ser  
1 5 10 15

Glu Trp Ile Ile Ser Pro Lys Ser Phe Asp Ala Tyr Tyr Cys Ser Gly  
20 25 30

Ala Cys Gln Phe Pro Met Pro Lys Ser Leu Lys Pro Ser Asn His Ala  
35 40 45

Thr Ile Gln Ser Ile Val Ala Arg Ala Val Gly Val Val Pro Gly Ile  
 50 55 60

Pro Glu Pro Cys Cys Val Pro Glu Lys Met Ser Ser Leu Ser Ile Leu  
 65 70 75 80

Phe Phe Asp Glu Asn Lys Asn Val Val Leu Lys Val Tyr Pro Asn Met  
 85 90 95

Thr Val Glu Ser Cys Ala Cys Arg  
 100

(2) INFORMATION FOR SEQ ID NO:27:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 102 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(vi) ORIGINAL SOURCE:

- (A) ORGANISM: HOMO SAPIENS

(ix) FEATURE:

- (A) NAME/KEY: Protein
- (B) LOCATION: 1..102
- (D) OTHER INFORMATION: /note= "BMP5"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:27:

Cys Lys Lys His Glu Leu Tyr Val Ser Phe Arg Asp Leu Gly Trp Gln  
 1 5 10 15

Asp Trp Ile Ile Ala Pro Glu Gly Tyr Ala Ala Phe Tyr Cys Asp Gly  
 20 25 30

Glu Cys Ser Phe Pro Leu Asn Ala His Met Asn Ala Thr Asn His Ala  
 35 40 45

Ile Val Gln Thr Leu Val His Leu Met Phe Pro Asp His Val Pro Lys  
 50 55 60

Pro Cys Cys Ala Pro Thr Lys Leu Asn Ala Ile Ser Val Leu Tyr Phe  
 65 70 75 80

Asp Asp Ser Ser Asn Val Ile Leu Lys Lys Tyr Arg Asn Met Val Val  
 85 90 95

Arg Ser Cys Gly Cys His  
 100

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(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 102 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(vi) ORIGINAL SOURCE:  
(A) ORGANISM: HOMO SAPIENS

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:28:

[illegible]

(i) SEQUENCE CHARACTERISTICS:  
(A) LENGTH: 102 amino acids  
(B) TYPE: amino acid  
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(ix) FEATURE:

- (A) NAME/KEY: Protein  
(B) LOCATION: 1..102  
(D) OTHER INFORMATION: /label= OPX  
/note= "WHEREIN EACH XAA IS INDEPENDENTLY SELECTED  
FROM A GROUP OF ONE OR MORE SPECIFIED AMINO ACIDS  
AS DEFINED IN THE SPECIFICATION (SECTION II.B.2.)"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:29:

[illegible]

(2) INFORMATION FOR SEQ ID NO:30:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 97 amino acids  
(B) TYPE: amino acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(ix) FEATURE:

- (A) NAME/KEY: Protein  
(B) LOCATION: 1..97  
(D) OTHER INFORMATION: /label= GENERIC-SEQ5  
/note= "WHEREIN EACH XAA IS INDEPENDENTLY SELECTED  
FROM A GROUP OF ONE OR MORE SPECIFIED AMINO ACIDS  
AS DEFINED IN THE SPECIFICATION."

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:30:

```

Leu Xaa Xaa Xaa Phe Xaa Xaa Xaa Gly Trp Xaa Xaa Trp Xaa Xaa Xaa
1 5 10 15
Pro Xaa Xaa Xaa Xaa Ala Xaa Tyr Cys Xaa Gly Xaa Cys Xaa Xaa Pro
 20 25 30
Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Asn His Ala Xaa Xaa Xaa Xaa Xaa
 35 40 45
Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Cys Cys Xaa Pro
 50 55 60
Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Leu Xaa Xaa Xaa Xaa Xaa Xaa Xaa
65 70 75 80
Val Xaa Leu Xaa Xaa Xaa Xaa Xaa Xaa Met Xaa Val Xaa Xaa Cys Xaa Cys
 85 90 95
Xaa

```

(2) INFORMATION FOR SEQ ID NO:31:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 102 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(ix) FEATURE:

- (A) NAME/KEY: Protein
- (B) LOCATION: 1..102
- (D) OTHER INFORMATION: /label= GENERIC-SEQ6  
/note= "WHEREIN EACH XAA IS INDEPENDENTLY SELECTED  
FROM A GROUP OF ONE OR MORE SPECIFIED AMINO ACIDS  
AS DEFINED IN THE SPECIFICATION. "

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:31:

```

Cys Xaa Xaa Xaa Xaa Leu Xaa Xaa Xaa Phe Xaa Xaa Xaa Gly Trp Xaa
1 5 10 15
Xaa Trp Xaa Xaa Xaa Pro Xaa Xaa Xaa Xaa Ala Xaa Tyr Cys Xaa Gly
 20 25 30
Xaa Cys Xaa Xaa Pro Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Asn His Ala
 35 40 45

```

00597517-002000

[illegible]

(2) INFORMATION FOR SEQ ID NO:32:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 1247 base pairs  
(B) TYPE: nucleic acid  
(C) STRANDEDNESS: single  
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(vi) ORIGINAL SOURCE:

- (A) ORGANISM: HOMO SAPIENS  
(F) TISSUE TYPE: BRAIN

(ix) FEATURE:

- (A) NAME/KEY: CDS  
(B) LOCATION: 84..1199  
(D) OTHER INFORMATION: /product= "GDF-1"  
/note= "GDF-1 CDNA"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:32:

|                                                                 |            |                                         |            |            |            |    |     |
|-----------------------------------------------------------------|------------|-----------------------------------------|------------|------------|------------|----|-----|
| GGGGACACCG                                                      | GCCCCGCCCT | CAGCCCACTG                              | GTCCCCGGGC | GCCGCGGACC | CTGCGCACTC |    | 60  |
| TCTGGTCATC                                                      | GCCTGGGAGG | AAG ATG CCA CCG CCG CAG CAA GGT CCC TGC |            |            |            |    | 110 |
|                                                                 |            | Met Pro Pro Pro Gln Gln Gly Pro Cys     |            |            |            |    |     |
|                                                                 |            | 1                                       |            | 5          |            |    |     |
| GGC CAC CAC CTC CTC CTC CTC CTG GCC CTG CTG CTG CCC TCG CTG CCC |            |                                         |            |            |            |    | 158 |
| Gly His His Leu Leu Leu Leu Leu Ala Leu Leu Leu Pro Ser Leu Pro |            |                                         |            |            |            |    |     |
| 10                                                              |            | 15                                      |            | 20         |            | 25 |     |
| CTG ACC CGC GCC CCC GTG CCC CCA GGC CCA GCC GCC GCC CTG CTC CAG |            |                                         |            |            |            |    | 206 |
| Leu Thr Arg Ala Pro Val Pro Pro Gly Pro Ala Ala Ala Leu Leu Gln |            |                                         |            |            |            |    |     |
|                                                                 |            | 30                                      |            | 35         |            | 40 |     |
| GCT CTA GGA CTG CGC GAT GAG CCC CAG GGT GCC CCC AGG CTC CGG CCG |            |                                         |            |            |            |    | 254 |
| Ala Leu Gly Leu Arg Asp Glu Pro Gln Gly Ala Pro Arg Leu Arg Pro |            |                                         |            |            |            |    |     |
|                                                                 |            | 45                                      |            | 50         |            | 55 |     |

|                                                                 |     |
|-----------------------------------------------------------------|-----|
| GTT CCC CCG GTC ATG TGG CGC CTG TTT CGA CGC CGG GAC CCC CAG GAG | 302 |
| Val Pro Pro Val Met Trp Arg Leu Phe Arg Arg Arg Asp Pro Gln Glu |     |
| 60 65 70                                                        |     |
| ACC AGG TCT GGC TCG CGG CGG ACG TCC CCA GGG GTC ACC CTG CAA CCG | 350 |
| Thr Arg Ser Gly Ser Arg Arg Thr Ser Pro Gly Val Thr Leu Gln Pro |     |
| 75 80 85                                                        |     |
| TGC CAC GTG GAG GAG CTG GGG GTC GCC GGA AAC ATC GTG CGC CAC ATC | 398 |
| Cys His Val Glu Glu Leu Gly Val Ala Gly Asn Ile Val Arg His Ile |     |
| 90 95 100 105                                                   |     |
| CCG GAC CGC GGT GCG CCC ACC CGG GCC TCG GAG CCT GTC TCG GCC GCG | 446 |
| Pro Asp Arg Gly Ala Pro Thr Arg Ala Ser Glu Pro Val Ser Ala Ala |     |
| 110 115 120                                                     |     |
| GGG CAT TGC CCT GAG TGG ACA GTC GTC TTC GAC CTG TCG GCT GTG GAA | 494 |
| Gly His Cys Pro Glu Trp Thr Val Val Phe Asp Leu Ser Ala Val Glu |     |
| 125 130 135                                                     |     |
| CCC GCT GAG CGC CCG AGC CGG GCC CGC CTG GAG CTG CGT TTC GCG GCG | 542 |
| Pro Ala Glu Arg Pro Ser Arg Ala Arg Leu Glu Leu Arg Phe Ala Ala |     |
| 140 145 150                                                     |     |
| GCG GCG GCG GCA GCC CCG GAG GGC GGC TGG GAG CTG AGC GTG GCG CAA | 590 |
| Ala Ala Ala Ala Ala Pro Glu Gly Gly Trp Glu Leu Ser Val Ala Gln |     |
| 155 160 165                                                     |     |
| GCG GGC CAG GGC GCG GGC GCG GAC CCC GGG CCG GTG CTG CTC CGC CAG | 638 |
| Ala Gly Gln Gly Ala Gly Ala Asp Pro Gly Pro Val Leu Leu Arg Gln |     |
| 170 175 180 185                                                 |     |
| TTG GTG CCC GCC CTG GGG CCG CCA GTG CGC GCG GAG CTG CTG GGC GCC | 686 |
| Leu Val Pro Ala Leu Gly Pro Pro Val Arg Ala Glu Leu Leu Gly Ala |     |
| 190 195 200                                                     |     |
| GCT TGG GCT CGC AAC GCC TCA TGG CCG CGC AGC CTC CGC CTG GCG CTG | 734 |
| Ala Trp Ala Arg Asn Ala Ser Trp Pro Arg Ser Leu Arg Leu Ala Leu |     |
| 205 210 215                                                     |     |
| GCG CTA CGC CCC CGG GCC CCT GCC GCC TGC GCG CGC CTG GCC GAG GCC | 782 |
| Ala Leu Arg Pro Arg Ala Pro Ala Ala Cys Ala Arg Leu Ala Glu Ala |     |
| 220 225 230                                                     |     |
| TCG CTG CTG CTG GTG ACC CTC GAC CCG CGC CTG TGC CAC CCC CTG GCC | 830 |
| Ser Leu Leu Leu Val Thr Leu Asp Pro Arg Leu Cys His Pro Leu Ala |     |
| 235 240 245                                                     |     |
| CGG CCG CGG CGC GAC GCC GAA CCC GTG TTG GGC GGC GGC CCC GGG GGC | 878 |
| Arg Pro Arg Arg Asp Ala Glu Pro Val Leu Gly Gly Gly Pro Gly Gly |     |
| 250 255 260 265                                                 |     |
| GCT TGT CGC GCG CGG CGG CTG TAC GTG AGC TTC CGC GAG GTG GGC TGG | 926 |
| Ala Cys Arg Ala Arg Arg Leu Tyr Val Ser Phe Arg Glu Val Gly Trp |     |
| 270 275 280                                                     |     |

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|                                                                   |      |
|-------------------------------------------------------------------|------|
| CAC CGC TGG GTC ATC GCG CCG CGC GGC TTC CTG GCC AAC TAC TGC CAG   | 974  |
| His Arg Trp Val Ile Ala Pro Arg Gly Phe Leu Ala Asn Tyr Cys Gln   |      |
| 285 290 295                                                       |      |
| GGT CAG TGC GCG CTG CCC GTC GCG CTG TCG GGG TCC GGG GGG CCG CCG   | 1022 |
| Gly Gln Cys Ala Leu Pro Val Ala Leu Ser Gly Ser Gly Gly Pro Pro   |      |
| 300 305 310                                                       |      |
| GCG CTC AAC CAC GCT GTG CTG CGC GCG CTC ATG CAC GCG GCC GCC CCG   | 1070 |
| Ala Leu Asn His Ala Val Leu Arg Ala Leu Met His Ala Ala Ala Pro   |      |
| 315 320 325                                                       |      |
| GGA GCC GCC GAC CTG CCC TGC TGC GTG CCC GCG CGC CTG TCG CCC ATC   | 1118 |
| Gly Ala Ala Asp Leu Pro Cys Cys Val Pro Ala Arg Leu Ser Pro Ile   |      |
| 330 335 340 345                                                   |      |
| TCC GTG CTC TTC TTT GAC AAC AGC GAC AAC GTG GTG CTG CGG CAG TAT   | 1166 |
| Ser Val Leu Phe Phe Asp Asn Ser Asp Asn Val Val Leu Arg Gln Tyr   |      |
| 350 355 360                                                       |      |
| GAG GAC ATG GTG GTG GAC GAG TGC GGC TGC CGC TAACCCGGGG CGGGCAGGGA | 1219 |
| Glu Asp Met Val Val Asp Glu Cys Gly Cys Arg                       |      |
| 365 370                                                           |      |
| CCCGGGCCCA ACAATAAATG CCGCGTGG                                    | 1247 |

(2) INFORMATION FOR SEQ ID NO:33:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 372 amino acids
- (B) TYPE: amino acid
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

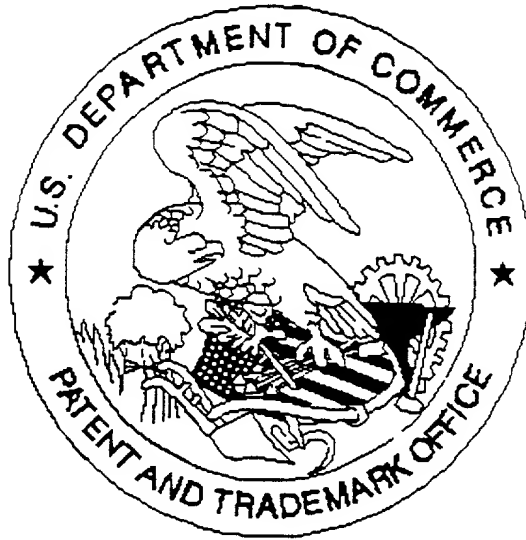
(xi) SEQUENCE DESCRIPTION: SEQ ID NO:33:

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |    |    |    |    |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|----|----|----|----|
| Met | Pro | Pro | Pro | Gln | Gln | Gly | Pro | Cys | Gly | His | His | Leu | Leu | Leu | Leu | 1  | 5  | 10 | 15 |
| Leu | Ala | Leu | Leu | Leu | Pro | Ser | Leu | Pro | Leu | Thr | Arg | Ala | Pro | Val | Pro | 20 | 25 | 30 |    |
| Pro | Gly | Pro | Ala | Ala | Ala | Leu | Leu | Gln | Ala | Leu | Gly | Leu | Arg | Asp | Glu | 35 | 40 | 45 |    |
| Pro | Gln | Gly | Ala | Pro | Arg | Leu | Arg | Pro | Val | Pro | Pro | Val | Met | Trp | Arg | 50 | 55 | 60 |    |
| Leu | Phe | Arg | Arg | Arg | Asp | Pro | Gln | Glu | Thr | Arg | Ser | Gly | Ser | Arg | Arg | 65 | 70 | 75 | 80 |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |  |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|--|
| Thr | Ser | Pro | Gly | Val | Thr | Leu | Gln | Pro | Cys | His | Val | Glu | Glu | Leu | Gly |  |
|     |     |     |     | 85  |     |     |     |     | 90  |     |     |     |     | 95  |     |  |
| Val | Ala | Gly | Asn | Ile | Val | Arg | His | Ile | Pro | Asp | Arg | Gly | Ala | Pro | Thr |  |
|     |     |     |     | 100 |     |     |     |     | 105 |     |     |     |     | 110 |     |  |
| Arg | Ala | Ser | Glu | Pro | Val | Ser | Ala | Ala | Gly | His | Cys | Pro | Glu | Trp | Thr |  |
|     |     |     |     | 115 |     |     |     |     | 120 |     |     |     |     | 125 |     |  |
| Val | Val | Phe | Asp | Leu | Ser | Ala | Val | Glu | Pro | Ala | Glu | Arg | Pro | Ser | Arg |  |
|     |     |     |     | 130 |     |     |     |     | 135 |     |     |     |     | 140 |     |  |
| Ala | Arg | Leu | Glu | Leu | Arg | Phe | Ala | Ala | Ala | Ala | Ala | Ala | Ala | Pro | Glu |  |
|     |     |     |     | 145 |     |     |     |     | 150 |     |     |     |     | 155 |     |  |
| Gly | Gly | Trp | Glu | Leu | Ser | Val | Ala | Gln | Ala | Gly | Gln | Gly | Ala | Gly | Ala |  |
|     |     |     |     | 165 |     |     |     |     | 170 |     |     |     |     | 175 |     |  |
| Asp | Pro | Gly | Pro | Val | Leu | Leu | Arg | Gln | Leu | Val | Pro | Ala | Leu | Gly | Pro |  |
|     |     |     |     | 180 |     |     |     |     | 185 |     |     |     |     | 190 |     |  |
| Pro | Val | Arg | Ala | Glu | Leu | Leu | Gly | Ala | Ala | Trp | Ala | Arg | Asn | Ala | Ser |  |
|     |     |     |     | 195 |     |     |     |     | 200 |     |     |     |     | 205 |     |  |
| Trp | Pro | Arg | Ser | Leu | Arg | Leu | Ala | Leu | Ala | Leu | Arg | Pro | Arg | Ala | Pro |  |
|     |     |     |     | 210 |     |     |     |     | 215 |     |     |     |     | 220 |     |  |
| Ala | Ala | Cys | Ala | Arg | Leu | Ala | Glu | Ala | Ser | Leu | Leu | Leu | Val | Thr | Leu |  |
|     |     |     |     | 225 |     |     |     |     | 230 |     |     |     |     | 235 |     |  |
| Asp | Pro | Arg | Leu | Cys | His | Pro | Leu | Ala | Arg | Pro | Arg | Arg | Asp | Ala | Glu |  |
|     |     |     |     | 245 |     |     |     |     | 250 |     |     |     |     | 255 |     |  |
| Pro | Val | Leu | Gly | Gly | Gly | Pro | Gly | Gly | Ala | Cys | Arg | Ala | Arg | Arg | Leu |  |
|     |     |     |     | 260 |     |     |     |     | 265 |     |     |     |     | 270 |     |  |
| Tyr | Val | Ser | Phe | Arg | Glu | Val | Gly | Trp | His | Arg | Trp | Val | Ile | Ala | Pro |  |
|     |     |     |     | 275 |     |     |     |     | 280 |     |     |     |     | 285 |     |  |
| Arg | Gly | Phe | Leu | Ala | Asn | Tyr | Cys | Gln | Gly | Gln | Cys | Ala | Leu | Pro | Val |  |
|     |     |     |     | 290 |     |     |     |     | 295 |     |     |     |     | 300 |     |  |
| Ala | Leu | Ser | Gly | Ser | Gly | Gly | Pro | Pro | Ala | Leu | Asn | His | Ala | Val | Leu |  |
|     |     |     |     | 305 |     |     |     |     | 310 |     |     |     |     | 315 |     |  |
| Arg | Ala | Leu | Met | His | Ala | Ala | Ala | Pro | Gly | Ala | Ala | Asp | Leu | Pro | Cys |  |
|     |     |     |     | 325 |     |     |     |     | 330 |     |     |     |     | 335 |     |  |



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